STIC Search Report
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STIC Database Tracking Number: 133116

TO: Dwayne C Jones **Location: REM-3B87&3C70** **Art Unit: 1614** **Thursday, September 23, 2004** **Case Serial Number: 10/763309**	**From: Barb O'Bryen** **Location: Biotech-Chem Library** **Remsen 1A69** **Phone: 571-272-2518** **barbara.obryen@uspto.gov**

Search Notes

"Please search claims 1,2,6, and 26"

sira
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What is Claimed:

1. A composition comprising citrulline and an Hmg-CoA reductase inhibitor.

2. The composition of claim 1, wherein said citrulline is L-citrulline.

3. The composition of claim 1, wherein said citrulline is a salt of L-citrulline.

4. The composition of claim 1, wherein said citrulline is L-citrulline hydrochloride.

5. The composition of claim 1, wherein the Hmg-CoA reductase inhibitor is pravastatin.

6. The composition of claim 1, wherein the Hmg-CoA reductase inhibitor is selected from the group consisting of atorvastatin, cerivastatin, simvastatin, lovastatin, compactin, fluvastatin, mevastatin, fluindostatin, velostatin and dalvastatin.

7. The composition of claim 1, wherein said Hmg-CoA reductase inhibitor enhances nitric oxide production.

8. The composition of claim 1, further comprising a pharmaceutical carrier.

9. The composition of claim 1, wherein the composition is formulated in a form of administration selected from the group consisting of intravenous, buccal, intracoronary, intra-arterial, intrapericardial, intramuscular, tropical, intranasal, rectal, sublingual, oral, subcutaneous, patch and inhalation.

10. A therapeutic composition comprising a therapeutically effective amount of citrulline and an Hmg-CoA reductase inhibitor.

11. The composition of claim 10, wherein said citrulline is L-citrulline.

12. The composition of claim 10, wherein said citrulline is a salt of L-citrulline.

13. The composition of claim 10, wherein said citrulline is L-citrulline hydrochloride.

14. The composition of claim 10, wherein the Hmg-CoA reductase inhibitor is pravastatin.

15. The composition of claim 10, wherein the Hmg-CoA reductase inhibitor is selected from the group consisting of atorvastatin, cerivastatin, simvastatin, lovastatin, compactin, fluvastatin, mevastatin, fluindostatin, velostatin and dalvastatin.

16. The composition of claim 10, further comprising a pharmaceutical carrier.

17. The composition of claim 10, wherein the composition is formulated in a form of administration selected from the group consisting of intravenous, buccal, intracoronary, intra-arterial, intrapericardial, intramuscular, tropical, intranasal, rectal, sublingual, oral, subcutaneous, patch and inhalation.

18. A method of treating a subject in need thereof comprising administering a composition comprising citrulline and an Hmg-CoA reductase inhibitor.

19. The method of claim 18, wherein the Hmg-CoA reductase inhibitor enhances nitric oxide synthase activity.

20. The method of claim 18, wherein said citrulline is L-citrulline.

21. The method of claim 18, wherein said citrulline is a salt of L-citrulline.

22. The method of claim 18, wherein said citrulline is L-citrulline hydrochloride.

23. The method of claim 18, wherein the Hmg-CoA reductase inhibitor is pravastatin.

24. The method of claim 18, wherein the Hmg-CoA reductase inhibitor is selected from the group consisting of atorvastatin, cerivastatin, simvastatin, lovastatin, compactin, fluvastatin, mevastatin, fluindostatin, velostatin and dalvastatin.

25. The method of claim 18, wherein the composition further comprises a pharmaceutical carrier.

26. A method of stimulating nitric oxide synthase comprising:

administering citrulline and an agonist of nitric oxide synthase.

27. The method of claim 26, wherein said citrulline is in excess to said agonist.

28. The method of claim 26, wherein a therapeutically effective amount of said citrulline is combined with a therapeutically effective amount of an Hmg-CoA reductase inhibitor prior to said administration.

29. The method of claim 29, wherein the Hmg-CoA reductase inhibitor is pravastatin.

30. The method of claim 29, wherein the Hmg-CoA reductase inhibitor is selected from the group consisting of atorvastatin, cerivastatin, simvastatin, lovastatin, compactin, fluvastatin, mevastatin, fluindostatin, velostatin and dalvastatin.

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BIBDATASHEET

Bib Data Sheet

CONFIRMATION NO. 6530

SERIAL NUMBER	FILING DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
10/763,309	01/23/2004 RULE	514	1614	126625.00801

APPLICANTS

Wayne H. Kaesemeyer, Augusta, GA;

** CONTINUING DATA **********

This application is a CON of 10/207,399 07/29/2002
which is a CIP of 09/226,580 01/07/1999 PAT 6,239,172

** FOREIGN APPLICATIONS **********

IF REQUIRED, FOREIGN FILING LICENSE GRANTED ** SMALL ENTITY **
** 04/27/2004

		STATE OR	SHEETS	TOTAL	INDEPENDENT
Foreign Priority claimed	☐ yes ☐ no	COUNTRY	DRAWING	CLAIMS	CLAIMS
35 USC 119 (a-d) conditions met	☐ yes ☐ no ☐ Met after Allowance	GA	17	30	4
Verified and Acknowledged	Examiner's Signature Initials				

ADDRESS
Pepper Hamilton LLP
Firm 21269
One Mellon Center, 50th Floor
500 Grant Street
Pittsburgh , PA
15219

TITLE
Pharmaceutical composition comprising citrulline

FILING FEE RECEIVED	FEES: Authority has been given in Paper No. _____ to charge/credit DEPOSIT ACCOUNT No. _____ for following:	☐ All Fees ☐ 1.16 Fees (Filing) ☐ 1.17 Fees (Processing Ext. of time) ☐ 1.18 Fees (Issue)

583		☐ Other _____
		☐ Credit

STIC SEARCH RESULTS FEEDBACK FORM

Biotech-Chem Library

Questions about the scope or the results of the search? Contact ***the searcher or contact***:

Mary Hale, Information Branch Supervisor
Remsen Bldg. 01 D86
571-272-2507

Voluntary Results Feedback Form

- *I am an examiner in Workgroup:* ☐ *Example: 1610*
- *Relevant prior art **found**, search results used as follows:*
  - ☐ 102 rejection
  - ☐ 103 rejection
  - ☐ Cited as being of interest.
  - ☐ Helped examiner better understand the invention.
  - ☐ Helped examiner better understand the state of the art in their technology.

Types of relevant prior art found:

- ☐ Foreign Patent(s)
- ☐ Non-Patent Literature
  (journal articles, conference proceedings, new product announcements etc.)

- *Relevant prior art **not found**:*
  - ☐ Results verified the lack of relevant prior art (helped determine patentability).
  - ☐ Results were not useful in determining patentability or understanding the invention.

Comments:

Drop off or send completed forms to STIC-Biotech-Chem Library Remsen Bldg.

National Library of Medicine - Medical Subject Headings

2004 MeSH

MeSH Descriptor Data

Return to Entry Page

MeSH Heading	Nitric-Oxide Synthase
Tree Number	D08.811.682.135.772
Tree Number	D08.811.682.608.550.772
Scope Note	An enzyme that catalyzes the conversion of L-arginine, NADPH, and oxygen to citrulline, nitric oxide, and NADP+. The enzyme found in brain, but not that induced in lung or liver by endotoxin, requires calcium. (From Enzyme Nomenclature, 1992) EC 1.14.13.39.
Entry Term	NO Synthase
Entry Term	EDRF Synthase
Entry Term	Endothelium-Derived Growth Factor Synthase
Entry Term	Guanylyl Cyclase-Activating Factor Synthase
Entry Term	Nitric-Oxide Synthetase
Allowable Qualifiers	AD AE AI AN BI BL CF CH CL CS CT DE DF DU EC GE HI IM IP ME PD PH PK PO RE SD SE ST TO TU UL UR
CAS Type 1 Name	L-Arginine,NADPH:oxygen oxidoreductase (nitric-oxide-forming)
Registry Number	EC 1.14.13.39
Previous Indexing	Amino Acid Oxidoreductases (1990-1995)
History Note	1996; use NITRIC-OXIDE SYNTHASE (NM) 1990-1995; for ENDOTHELIUM-DERIVED GROWTH FACTOR SYNTHASE use NITRIC-OXIDE SYNTHASE (NM) 1991-2000
Unique ID	D019001

MeSH Tree Structures

Enzymes and Coenzymes [D08]
  Enzymes [D08.811]
    Oxidoreductases [D08.811.682]

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STRUCTURE FILE UPDATES:   22 SEP 2004  HIGHEST RN 749824-02-0
DICTIONARY FILE UPDATES:  22 SEP 2004  HIGHEST RN 749824-02-0

TSCA INFORMATION NOW CURRENT THROUGH MAY 21, 2004

  Please note that search-term pricing does apply when
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Crossover limits have been increased.  See HELP CROSSOVER for details.

Experimental and calculated property data are now available. For more
information enter HELP PROP at an arrow prompt in the file or refer
to the file summary sheet on the web at:
http://www.cas.org/ONLINE/DBSS/registryss.html



L6   ANSWER 1 OF 2  REGISTRY  COPYRIGHT 2004 ACS on STN
RN   28044-09-9  REGISTRY
CN   L-Ornithine, N5-(aminocarbonyl)-, hydrochloride (9CI)  (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN   Ornithine, N5-carbamoyl-, hydrochloride, L- (8CI)
OTHER NAMES:
CN   L-Citrulline hydrochloride
FS   STEREOSEARCH
MF   C6 H13 N3 O3 . x Cl H
LC   STN Files:   CA, CAPLUS
DT.CA  CAplus document type:  Journal
RL.NP  Roles from non-patents:  BIOL (Biological study)
CRN  (372-75-8)

Absolute stereochemistry.
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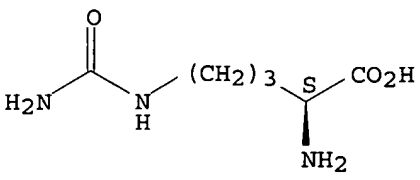


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          ●x  HCl

               1 REFERENCES IN FILE CA (1907 TO DATE)
               1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

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RN   372-75-8  REGISTRY
CN   L-Ornithine, N5-(aminocarbonyl)- (9CI)  (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN   Ornithine, N5-carbamoyl-, L- (8CI)
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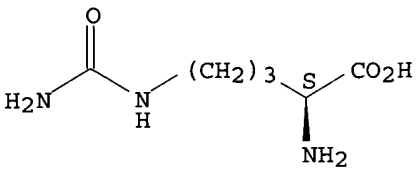
OTHER NAMES:
CN .alpha.-Amino-.delta.-ureidovaleric acid
CN .delta.-Ureidonorvaline
CN **Citrulline**
CN **L-Citrulline**
CN N.delta.-Carbamylornithine
CN N5-Carbamoyl-L-ornithine
CN NSC 27425
FS STEREOSEARCH
MF C6 H13 N3 O3
CI COM
LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CEN, CHEMCATS, CHEMINFORMRX, CHEMLIST, CIN, CSCHEM, DDFU, DRUGU, EMBASE, HODOC*, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, MRCK*, MSDS-OHS, NAPRALERT, NIOSHTIC, PIRA, PROMT, PS, SPECINFO, TOXCENTER, USPAT2, USPATFULL, VETU
(*File contains numerically searchable property data)
Other Sources: EINECS**, NDSL**, TSCA**
(**Enter CHEMLIST File for up-to-date regulatory information)
DT.CA CAplus document type: Conference; Dissertation; Journal; Patent; Report
RL.P Roles from patents: ANST (Analytical study); BIOL (Biological study); FORM (Formation, nonpreparative); OCCU (Occurrence); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses); NORL (No role in record)
RLD.P Roles for non-specific derivatives from patents: ANST (Analytical study); BIOL (Biological study); PREP (Preparation); PROC (Process); PRP (Properties); USES (Uses)
RL.NP Roles from non-patents: ANST (Analytical study); BIOL (Biological study); FORM (Formation, nonpreparative); MSC (Miscellaneous); OCCU (Occurrence); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses); NORL (No role in record)
RLD.NP Roles for non-specific derivatives from non-patents: ANST (Analytical study); BIOL (Biological study); FORM (Formation, nonpreparative); OCCU (Occurrence); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses)

Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

3609 REFERENCES IN FILE CA (1907 TO DATE)
58 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
3619 REFERENCES IN FILE CAPLUS (1907 TO DATE)
69 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

=> d ide l8; d ide l9

L8 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2004 ACS on STN
RN **9028-35-7** REGISTRY
CN Reductase, hydroxymethylglutaryl coenzyme A (reduced nicotinamide adenine dinucleotide phosphate) (9CI) (CA INDEX NAME)
OTHER NAMES:

CN .beta.-Hydroxy-.beta.-methylglutaryl coenzyme A reductase
CN .beta.-Hydroxy-.beta.-methylglutaryl-CoA reductase
CN 3-Hydroxy-3-methylglutaryl CoA reductase
CN 3-Hydroxy-3-methylglutaryl CoA reductase(NADPH)
CN 3-Hydroxy-3-methylglutaryl coenzyme A reductase
CN E.C. 1.1.1.34
CN HMG-CoA reductase
CN Hydroxymethylglutaryl CoA reductase (NADPH)
CN Hydroxymethylglutaryl coenzyme A reductase
CN Hydroxymethylglutaryl coenzyme A reductase (NADPH)
CN Hydroxymethylglutaryl coenzyme A reductase (reduced nicotinamide adenine dinucleotide phosphate)
CN Hydroxymethylglutaryl-CoA reductase
CN NADPH-hydroxymethylglutaryl-CoA reductase
CN S-3-Hydroxy-3-methylglutaryl-CoA reductase
DR 99725-05-0
MF Unspecified
CI MAN
LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CABA, CAPLUS, CASREACT, CEN, CIN, DIOGENES, EMBASE, PIRA, PROMT, TOXCENTER, USPAT2, USPATFULL
DT.CA CAplus document type: Book; Conference; Dissertation; Journal; Patent; Report
RL.P Roles from patents: ANST (Analytical study); BIOL (Biological study); MSC (Miscellaneous); OCCU (Occurrence); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses)
RLD.P Roles for non-specific derivatives from patents: BIOL (Biological study); MSC (Miscellaneous); PREP (Preparation); USES (Uses)
RL.NP Roles from non-patents: ANST (Analytical study); BIOL (Biological study); FORM (Formation, nonpreparative); MSC (Miscellaneous); OCCU (Occurrence); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses); NORL (No role in record)
RLD.NP Roles for non-specific derivatives from non-patents: ANST (Analytical study); BIOL (Biological study); PREP (Preparation); PROC (Process); PRP (Properties); USES (Uses)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
5730 REFERENCES IN FILE CA (1907 TO DATE)
23 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
5762 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L9 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2004 ACS on STN
RN **125978-95-2** REGISTRY
CN Synthase, nitric oxide (9CI) (CA INDEX NAME)
OTHER NAMES:
CN E.C. 1.14.13.39
CN Nitric oxide synthase
CN Nitric oxide synthetase
CN NO synthase
MF Unspecified
CI MAN
SR CA
LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CAPLUS, CEN, CHEMCATS, CIN, CSCHEM, EMBASE, IPA, PROMT, TOXCENTER, USPAT2, USPATFULL
DT.CA CAplus document type: Book; Conference; Dissertation; Journal; Patent; Report
RL.P Roles from patents: ANST (Analytical study); BIOL (Biological study); FORM (Formation, nonpreparative); MSC (Miscellaneous); OCCU

(Occurrence); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses)

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RL.NP Roles from non-patents: ANST (Analytical study); BIOL (Biological study); FORM (Formation, nonpreparative); MSC (Miscellaneous); OCCU (Occurrence); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses)

RLD.NP Roles for non-specific derivatives from non-patents: ANST (Analytical study); BIOL (Biological study); FORM (Formation, nonpreparative); OCCU (Occurrence); PREP (Preparation); PROC (Process); PRP (Properties); USES (Uses)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

19425 REFERENCES IN FILE CA (1907 TO DATE)

64 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA

19461 REFERENCES IN FILE CAPLUS (1907 TO DATE)

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=> fil capl; d que l23
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FILE COVERS 1907 - 23 Sep 2004  VOL 141 ISS 13
FILE LAST UPDATED: 22 Sep 2004  (20040922/ED)

  This file contains CAS Registry Numbers for easy and accurate
  substance identification.

'OBI' IS DEFAULT SEARCH FIELD FOR 'CAPLUS' FILE


L3             1 SEA FILE=REGISTRY ABB=ON  CITRULLINE/CN
L4             1 SEA FILE=REGISTRY ABB=ON  L-CITRULLINE/CN
L5             1 SEA FILE=REGISTRY ABB=ON  "L-CITRULLINE HYDROCHLORIDE"/CN
L6             2 SEA FILE=REGISTRY ABB=ON  (L3 OR L4 OR L5)
L8             1 SEA FILE=REGISTRY ABB=ON  9028-35-7
L10            7 SEA FILE=REGISTRY ABB=ON  ATORVASTATIN?/CN
L11            3 SEA FILE=REGISTRY ABB=ON  CERIVASTATIN?/CN
L12            7 SEA FILE=REGISTRY ABB=ON  SIMVASTATIN?/CN
L13            9 SEA FILE=REGISTRY ABB=ON  LOVASTATIN/CN OR ("LOVASTATIN
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                  OR ("LOVASTATIN HEMICALCIUM"/CN OR "LOVASTATIN LACTONE"/CN)
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L14            5 SEA FILE=REGISTRY ABB=ON  COMPACTIN/CN OR ("COMPACTIN ACID"/CN
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L17            1 SEA FILE=REGISTRY ABB=ON  FLUINDOSTATIN/CN
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L19            1 SEA FILE=REGISTRY ABB=ON  DALVASTATIN/CN
L20         3622 SEA FILE=CAPLUS ABB=ON  L6
L21         5188 SEA FILE=CAPLUS ABB=ON  (L10 OR L11 OR L12 OR L13 OR L14 OR
                 L15 OR L16 OR L17 OR L18 OR L19)
L22         3147 SEA FILE=CAPLUS ABB=ON  L8(L)INHIB?/OBI
L23            2 SEA FILE=CAPLUS ABB=ON  L20 AND (L21 OR L22)


=> fil uspatf; d que l46

FILE 'USPATFULL' ENTERED AT 12:52:38 ON 23 SEP 2004
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FILE COVERS 1971 TO PATENT PUBLICATION DATE: 23 Sep 2004 (20040923/PD)
FILE LAST UPDATED: 23 Sep 2004 (20040923/ED)
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HIGHEST GRANTED PATENT NUMBER: US6795973
HIGHEST APPLICATION PUBLICATION NUMBER: US2004187181
CA INDEXING IS CURRENT THROUGH 23 Sep 2004 (20040923/UPCA)
ISSUE CLASS FIELDS (/INCL) CURRENT THROUGH: 23 Sep 2004 (20040923/PD)
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Jun 2004
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Jun 2004

>>> USPAT2 is now available. USPATFULL contains full text of the <<<
>>> original, i.e., the earliest published granted patents or <<<
>>> applications. USPAT2 contains full text of the latest US <<<
>>> publications, starting in 2001, for the inventions covered in <<<
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>>> <<<
>>> Use USPATALL when searching terms such as patent assignees, <<<
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>>> the earliest to the latest publication. <<<

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L3            1 SEA FILE=REGISTRY ABB=ON  CITRULLINE/CN
L4            1 SEA FILE=REGISTRY ABB=ON  L-CITRULLINE/CN
L5            1 SEA FILE=REGISTRY ABB=ON  "L-CITRULLINE HYDROCHLORIDE"/CN
L6            2 SEA FILE=REGISTRY ABB=ON  (L3 OR L4 OR L5)
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L10           7 SEA FILE=REGISTRY ABB=ON  ATORVASTATIN?/CN
L11           3 SEA FILE=REGISTRY ABB=ON  CERIVASTATIN?/CN
L12           7 SEA FILE=REGISTRY ABB=ON  SIMVASTATIN?/CN
L13           9 SEA FILE=REGISTRY ABB=ON  LOVASTATIN/CN OR ("LOVASTATIN
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L14           5 SEA FILE=REGISTRY ABB=ON  COMPACTIN/CN OR ("COMPACTIN ACID"/CN
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L41         181 SEA FILE=USPATFULL ABB=ON  L6
L42         668 SEA FILE=USPATFULL ABB=ON  L8
L43         606 SEA FILE=USPATFULL ABB=ON  L42(L)INHIB?/IT
L45         826 SEA FILE=USPATFULL ABB=ON  (L10 OR L11 OR L12 OR L13 OR L14 OR
                L15 OR L16 OR L17 OR L18 OR L19)
L46           2 SEA FILE=USPATFULL ABB=ON  L41 AND (L43 OR L45)
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=> fil medl; d que l63

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FILE 'MEDLINE' ENTERED AT 12:52:39 ON 23 SEP 2004

 FILE LAST UPDATED: 22 SEP 2004 (20040922/UP). FILE COVERS 1951 TO DATE.

 On February 29, 2004, the 2004 MeSH terms were loaded. See HELP RLOAD
 for details. OLDMEDLINE now back to 1951.

 MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the
 MeSH 2004 vocabulary. See http://www.nlm.nih.gov/mesh/ and
 http://www.nlm.nih.gov/pubs/techbull/nd03/nd03_mesh.html for a
 description of changes.

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.


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L13             9 SEA FILE=REGISTRY ABB=ON  LOVASTATIN/CN OR ("LOVASTATIN
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                  E"/CN) OR "LOVASTATIN DIMER"/CN OR "LOVASTATIN DIOL LACTONE"/CN
                   OR ("LOVASTATIN HEMICALCIUM"/CN OR "LOVASTATIN LACTONE"/CN)
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L18             1 SEA FILE=REGISTRY ABB=ON  VELOSTATIN/CN
L19             1 SEA FILE=REGISTRY ABB=ON  DALVASTATIN/CN
L59          2100 SEA FILE=MEDLINE ABB=ON  CITRULLINE/CT
L60          8796 SEA FILE=MEDLINE ABB=ON  HYDROXYMETHYLGLUTARYL-COA REDUCTASE
                  INHIBITORS+NT/CT
L61          5134 SEA FILE=MEDLINE ABB=ON  (L10 OR L11 OR L12 OR L13 OR L14 OR
                  L15 OR L16 OR L17 OR L18 OR L19)
L63             1 SEA FILE=MEDLINE ABB=ON  L59 AND (L60 OR L61)


=> fil embase; d que l84

FILE 'EMBASE' ENTERED AT 12:52:40 ON 23 SEP 2004
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 FILE COVERS 1974 TO 16 Sep 2004 (20040916/ED)

 EMBASE has been reloaded. Enter HELP RLOAD for details.

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.


L10             7 SEA FILE=REGISTRY ABB=ON  ATORVASTATIN?/CN
L11             3 SEA FILE=REGISTRY ABB=ON  CERIVASTATIN?/CN
L12             7 SEA FILE=REGISTRY ABB=ON  SIMVASTATIN?/CN
L13             9 SEA FILE=REGISTRY ABB=ON  LOVASTATIN/CN OR ("LOVASTATIN
                  ACID"/CN OR "LOVASTATIN ACID AMIDE"/CN OR "LOVASTATIN BUTYLAMID
                  E"/CN) OR "LOVASTATIN DIMER"/CN OR "LOVASTATIN DIOL LACTONE"/CN
                   OR ("LOVASTATIN HEMICALCIUM"/CN OR "LOVASTATIN LACTONE"/CN)
                  OR ("LOVASTATIN PIPERIDINAMIDE"/CN OR "LOVASTATIN SODIUM
                  SALT"/CN)
```

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L14           5 SEA FILE=REGISTRY ABB=ON  COMPACTIN/CN OR ("COMPACTIN ACID"/CN
                OR "COMPACTIN DIOL LACTONE"/CN) OR "COMPACTIN SODIUM SALT"/CN
L15           3 SEA FILE=REGISTRY ABB=ON  FLUVASTATIN?/CN
L16           1 SEA FILE=REGISTRY ABB=ON  MEVASTATIN/CN
L17           1 SEA FILE=REGISTRY ABB=ON  FLUINDOSTATIN/CN
L18           1 SEA FILE=REGISTRY ABB=ON  VELOSTATIN/CN
L19           1 SEA FILE=REGISTRY ABB=ON  DALVASTATIN/CN
L75        2121 SEA FILE=EMBASE ABB=ON  CITRULLINE/CT OR CITRULLINE DERIVATIVE/
                CT
L76       19652 SEA FILE=EMBASE ABB=ON  HYDROXYMETHYLGLUTARYL COENZYME A
                REDUCTASE INHIBITOR+NT/CT
L77       13866 SEA FILE=EMBASE ABB=ON  (L10 OR L11 OR L12 OR L13 OR L14 OR
                L15 OR L16 OR L17 OR L18 OR L19)
L83         117 SEA FILE=EMBASE ABB=ON  L75(L)(DT OR PD OR AD OR DO OR PK)/CT
L84           1 SEA FILE=EMBASE ABB=ON  L83 AND (L76 OR L77)


=> fil DRUGU, PASCAL, BIOSIS, WPIDS; d que l101

FILE 'DRUGU' ENTERED AT 12:52:41 ON 23 SEP 2004
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L95        6253 SEA CITRULLINE OR NSC27425 OR NSC 27425
L96          24 SEA (AMINOCARBONYL OR AMINO CARBONYL OR CARBAMOYL OR CARBAMYL)(
                1W) ORNITHINE OR UREIDONORVALINE OR UREIDO NORVALINE
L97       37355 SEA ATORVASTATIN# OR CERIVASTATIN# OR SIMVASTATIN# OR LOVASTATI
                N# OR COMPACTIN# OR FLUVASTATIN# OR MEVASTATIN#
L98          67 SEA FLUINDOSTATIN# OR VELOSTATIN# OR DALVASTATIN#
L100      16705 SEA ((HMG OR HYDROXYMETHYLGLUTARYL OR HYDROXY(1W)(METHYLGLUTARY
                L OR METHYL GLUTARYL))(W)(COA OR (COENZYME OR CO ENZYME)(W)
                A)(W) REDUCTASE)(3A)(INHIB? OR ANTAG? OR BLOCK?)
L101         13 SEA (L95 OR L96) AND ((L97 OR L98) OR L100)


=> dup rem l63,l23,l101,l84,l46

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FILE 'EMBASE' ENTERED AT 12:52:43 ON 23 SEP 2004

FILE 'USPATFULL' ENTERED AT 12:52:43 ON 23 SEP 2004

PROCESSING COMPLETED FOR L63
PROCESSING COMPLETED FOR L23
PROCESSING COMPLETED FOR L101
PROCESSING COMPLETED FOR L84
PROCESSING COMPLETED FOR L46
L109 14 DUP REM L63 L23 L101 L84 L46 (5 DUPLICATES REMOVED)
ANSWER '1' FROM FILE MEDLINE
ANSWERS '2-3' FROM FILE CAPLUS
ANSWERS '4-5' FROM FILE DRUGU
ANSWERS '6-10' FROM FILE PASCAL
ANSWERS '11-12' FROM FILE BIOSIS
ANSWER '13' FROM FILE EMBASE
ANSWER '14' FROM FILE USPATFULL

=> d iall 1; d ibib ed ab hitrn 2-3; d iall 4-13; d ibib ab hitrn 14

L109 ANSWER 1 OF 14 MEDLINE on STN
ACCESSION NUMBER: 2003418929 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12958617
TITLE: Platelet hyperactivity after statin treatment discontinuation.
AUTHOR: Puccetti Luca; Pasqui Anna Laura; Pastorelli Marcello; Bova Giovanni; Di Renzo Michela; Leo Alessandro; Cercignani Michela; Palazzuoli Alberto; Auteri Alberto; Bruni Fulvio
CORPORATE SOURCE: Department of Clinical Medicine and Immunological Sciences, Internal Medicine Division, Policlinico Le Scotte, V. le Bracci, 53100, Siena, Italy.. puccetti@unisi.it
SOURCE: Thrombosis and haemostasis, (2003 Sep) 90 (3) 476-82. Journal code: 7608063. ISSN: 0340-6245.
PUB. COUNTRY: Germany: Germany, Federal Republic of
DOCUMENT TYPE: (CLINICAL TRIAL)
(CONTROLLED CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200405
ENTRY DATE: Entered STN: 20030906
Last Updated on STN: 20040522
Entered Medline: 20040521

ABSTRACT:
Hydroxymethyl-glutaryl-CoA-reductase inhibitors (statins) reduce cardiovascular events by cholesterol lowering as well as by non-lipid related actions. Among them, the modulation of platelet activity could play a relevant role in vascular protection. Furthermore withdrawal of statins has been associated with increased cardiovascular event rate. The aim of our study was to evaluate platelet activity after cerivastatin discontinuation in eighteen subjects that did not accept other drugs and in sixteen subjects continuing treatment with simvastatin. Fourteen subjects at the end of the discontinuation period decided to receive other drugs (simvastatin) and they were evaluted six weeks later. We measured complete lipid profile by the chromogenic method (LDL-C was calculated); oxidized-LDL (ox-LDL; ELISA), platelet P-selectin (P-sel)

expression (flow cytometry detection), platelet aggregation (% change of transmitted light), intracellular citrullin production (iCit; HPLC) as an indicator of intracellular NO synthase activity at baseline and 7, 14, 28, 60 days after statin discontinuation. P-sel expression and platelet aggregation were increased at 14 days ($p < 0.001$ and $p < 0.05$) in association with raised ox-LDL ($r = 0.30$, $p < 0.05$) and decreased iCit ($r = 0.53$, $p < 0.01$). Increased LDL-C was related to P-sel and platelet aggregation at 28 days ($r = 0.30$, $p < 0.05$). Subjects continuing statin treatment had no significant changes of P-sel at 28 ($p = 0.221$) and 60 days ($p = 0.238$). Subjects treated with simvastatin after 60 days of diet showed a significant reduction of P-sel and platelet aggregation after six weeks of treatment ($p < 0.01$). Our data suggest a platelet hyperactivation state in the second week after statin discontinuation which is partially related to raised LDL-C. Such a finding could participate in the increased cardiovascular event rate after statin discontinuation.

CONTROLLED TERM: Check Tags: Female; Human; Male
Adult
Blood Platelets: DE, drug effects
Blood Platelets: ME, metabolism
Blood Platelets: PH, physiology
Citrulline: BI, biosynthesis
Diet
***Hydroxymethylglutaryl-CoA Reductase Inhibitors: AE, adverse effects**
Hydroxymethylglutaryl-CoA Reductase Inhibitors: TU, therapeutic use
Hypercholesterolemia: BL, blood
Hypercholesterolemia: DT, drug therapy
Lipids: BL, blood
Lipoproteins, LDL: BL, blood
Middle Aged
Nitric-Oxide Synthase: ME, metabolism
P-Selectin: AN, analysis
*Platelet Activation: DE, drug effects
Platelet Aggregation: DE, drug effects
*Pyridines: AE, adverse effects
Pyridines: TU, therapeutic use
*Substance Withdrawal Syndrome: BL, blood

CAS REGISTRY NO.: **143201-11-0 (cerivastatin)**; 372-75-8 (Citrulline)

CHEMICAL NAME: 0 (Hydroxymethylglutaryl-CoA Reductase Inhibitors); 0 (Lipids); 0 (Lipoproteins, LDL); 0 (P-Selectin); 0 (Pyridines); 0 (oxidized low density lipoprotein); EC 1.14.13.39 (Nitric-Oxide Synthase)

L109 ANSWER 2 OF 14 CAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 1

ACCESSION NUMBER: 2004:451474 CAPLUS

DOCUMENT NUMBER: 141:1258

TITLE: Nitrosated compounds in methods of treating vascular diseases characterized by nitric oxide insufficiency

INVENTOR(S): Loscalzo, Joseph; Vita, Joseph A.; Loberg, Michael D.; Worcel, Manuel

PATENT ASSIGNEE(S): USA

SOURCE: U.S. Pat. Appl. Publ., 23 pp., Cont.-in-part of U.S. Ser. No. 679,257.
CODEN: USXXCO

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 5

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
US 2004105850	A1	20040603	US 2003-692724		20031027
US 6635273	B1	20031021	US 2000-697317		20001027
US 2004071766	A1	20040415	US 2003-679257		20031007
PRIORITY APPLN. INFO.:			US 1999-162230P	P	19991029
			US 2000-179020P	P	20000131
			US 2000-697317	A1	20001027
			US 2003-679257	A2	20031007

OTHER SOURCE(S): MARPAT 141:1258
ED Entered STN: 04 Jun 2004
AB The invention provides methods of treating and/or preventing vascular diseases characterized by nitric oxide insufficiency by administering a therapeutically effective amt. of at least one nitrosated angiotensin-converting enzyme inhibitor, nitrosated beta-adrenergic blocker, nitrosated cholesterol reducer, nitrosated calcium channel blocker, nitrosated endothelin antagonist, nitrosated angiotensin II receptor antagonist, nitrosated renin inhibitor, and optionally at least one compd. used to treat cardiovascular diseases and/or at least one antioxidant, or a pharmaceutically acceptable salt thereof, and/or at least one compd. that donates, transfers or releases nitric oxide, elevates endogenous levels of endothelium-derived relaxing factor, stimulates endogenous synthesis of nitric oxide or is a substrate for nitric oxide synthase. The antioxidant may preferably be a hydralazine compd. or a pharmaceutically acceptable salt thereof. The compd. that donates, transfers or releases nitric oxide, elevates endogenous levels of endothelium-derived relaxing factor, stimulates endogenous synthesis of nitric oxide or is a substrate for nitric oxide synthase may preferably be isosorbide dinitrate and/or isosorbide mononitrate. The vascular diseases characterized by nitric oxide insufficiency include a cardiovascular disease and a disease resulting from oxidative stress. Nitric oxide action was shown to be impaired in the microvasculature of black hypertensive patients to a greater extent than in white hypertensive patients.
IT **372-75-8**, L-Citrulline
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(as further therapeutic agent; nitrosated compds. in methods of treating vascular diseases characterized by nitric oxide insufficiency)
IT **75330-75-5D**, Lovastatin, nitrosated compds. **79902-63-9D**, Simvastatin, nitrosated compds. **93957-54-1D**, Fluvastatin, nitrosated compds. **134523-00-5D**, Atorvastatin, nitrosated compds. **145599-86-6D**, Cerivastatin, nitrosated compds.
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(nitrosated compds. in methods of treating vascular diseases characterized by nitric oxide insufficiency)

L109 ANSWER 3 OF 14 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2004:41217 CAPLUS
DOCUMENT NUMBER: 140:111135
TITLE: Preparation of nitrosated nonsteroidal antiinflammatory compounds
INVENTOR(S): Earl, Richard A.; Ezawa, Maiko; Fang, Xinqin; Garvey, David S.; Gaston, Ricky D.; Khanapure, Subhash P.; Letts, Gordon L.; Lin, Chia-En; Ranatunge, Ramani R.; Richardson, Stewart K.; Schroeder, Joseph D.; Stevenson, Cheri A.; Wey, Shiow-Jyi
PATENT ASSIGNEE(S): Nitromed, Inc., USA
SOURCE: PCT Int. Appl., 145 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004004648	A2	20040115	WO 2003-US21026	20030703
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2004024057	A1	20040205	US 2003-612014	20030703
PRIORITY APPLN. INFO.:			US 2002-393111P P	20020703
			US 2002-397979P P	20020724
			US 2002-418353P P	20021016
			US 2003-449798P P	20030226
			US 2003-456182P P	20030321

OTHER SOURCE(S): MARPAT 140:111135
ED Entered STN: 18 Jan 2004
AB Title compds. RnRmHC-CO-X [Rm = H, alkyl; Rn = 4-((thiophen-2-yl)carbonyl)phenyl, 3-(benzoyl)phenyl, etc.; X = Y-alkyl-aryl, etc.; Y = O, S; I] are prepd. For instance, naproxen is coupled to 2,2'-thiodiethanol (CH2Cl2, DMAP, EDCI) and treated with Ac2O/HNO3 at 0.degree. to give II. I are nitrosated nonsteroidal antiinflammatory drugs (NSAIDs) used alone or are combined with one compd. that donates, transfers or releases nitric oxide, stimulates endogenous synthesis of nitric oxide, elevates endogenous levels of endothelium-derived relaxing factor or is a substrate for nitric oxide synthase. The invention provides methods for treating inflammation, pain, fever, gastrointestinal disorders, etc.
IT **372-75-8**, Citrulline
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(combination pharmaceutical; prepn. of naproxen-derived nitrosated antiinflammatory compds.)
IT **9028-35-7**, 3-Hydroxy-3-methylglutaryl coenzyme A reductase
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**inhibitor**, combination pharmaceutical; prepn. of naproxen-derived nitrosated antiinflammatory compds.)

L109 ANSWER 4 OF 14 DRUGU COPYRIGHT 2004 THOMSON DERWENT on STN
ACCESSION NUMBER: 2002-34823 DRUGU P
TITLE: The influence of lipid-lowering treatment on nitric oxide synthesis in endothelial cells.
AUTHOR: Korzh I V
CORPORATE SOURCE: Univ.Kharkov-Med.
LOCATION: Kharkov, Ukraine
SOURCE: ; 1581B ; Atherosclerosis Supplements (3, No. 2, 142, 2002)
AVAIL. OF DOC.: Kharkov Medical University, Kharkov, Ukraine.
LANGUAGE: English
DOCUMENT TYPE: Journal

ABSTRACT:

In-vitro, **simvastatin** restored calcium-dependent nitric oxide (NO) release in human umbilical vein endothelial cells (HUVEC). This protective effect was mediated not only by normalization of lipid metabolism but also by an increase in endothelial constitutive nitric oxide synthase (cNOS) activity. (conference abstract: 73rd Congress of the European Atherosclerosis Society, Salzburg, Austria, 2002).

SECTION HEADING: P Pharmacology

CLASSIF. CODE: 58 Vasoactive

CONTROLLED TERM:
[01] **SIMVASTATIN** *PH; SYNVINOLI.*RN; IN-VITRO *FT; HUMAN *FT; UMBILICAL *FT; VEIN *FT; ENDOTHELIUM *FT; ANTIARTERIOSCLEROTIC *FT; MODE-OF-ACT. *FT; NITRIC-OXIDE *FT; RELEASE *FT; VESSEL *FT; ANTIARTERIOSCLEROTICS *FT; **HMG-COA-REDUCTASE-INHIBITORS** *FT; PH *FT

CAS REGISTRY NO.: 79902-63-9
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature

L109 ANSWER 5 OF 14 DRUGU COPYRIGHT 2004 THOMSON DERWENT on STN
ACCESSION NUMBER: 1998-12242 DRUGU B P
TITLE: **Simvastatin** pretreatment protects from focal cerebral ischemia.
AUTHOR: Endres M; Laufs U; Nakamura T; Huang Z; Liao J; Moskowitz M A
CORPORATE SOURCE: Harvard-Med.Sch.
LOCATION: Boston, Mass., USA
SOURCE: Stroke (29, No. 1, 325, 1998)
CODEN: SJCCA7 ISSN: 0039-2499
AVAIL. OF DOC.: Stroke Laboratory, Mass. General Hosp., Harvard Medical School, Boston, MA, U.S.A.
LANGUAGE: English
DOCUMENT TYPE: Journal

ABSTRACT:

A study was undertaken in mice to test the theory that **simvastatin** (SIM) up-regulates endothelial nitric oxide synthase (eNOS) activity in-vivo and reduces focal cerebral ischemic damage. SIM-pre-treated animals had smaller infarcts than untreated controls and this effect sustained for a couple of days. Moreover, neurological deficits were improved. Physiological parameters and plasma cholesterol levels did not differ between groups. NOS activity in aortas from SIM-treated animals was higher than in untreated controls. These results indicate that statins protect from acute cerebral ischemia possibly by a cerebrovascular mechanism through up-regulation of eNOS. (conference abstract).

SECTION HEADING: B Biochemistry
P Pharmacology

CLASSIF. CODE: 14 Enzyme Inhibitors
22 Endogenous Compounds
58 Vasoactive
59 CNS and Motor

CONTROLLED TERM:
[01] **SIMVASTATIN** *PH; CEREBRAL *OC; ISCHEMIA *OC;

APOPLEXY *OC; CEREBROVASCULAR-DISEASE *OC; SYNVINOLI *RN; MOUSE *FT; IN-VIVO *FT; S.C. *FT; BLOOD-PRESSURE *FT; BLOOD-PLASMA *FT; CHOLESTEROL *FT; LIPID-METAB. *FT; EC-1.14.13.39 *FT; AORTA *FT; **HMG-COA-REDUCTASE-INHIBITOR** *FT; LAB.ANIMAL *FT; INJECTION *FT; HEMODYNAMICS *FT; NITRIC-OXIDE-SYNTHASE *FT; VESSEL *FT; ARTERY *FT; ANTIARTERIOSCLEROTICS *FT; **HMG-COA-REDUCTASE-INHIBITORS** *FT; PH *FT

CAS REGISTRY NO.: 79902-63-9
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature

L109 ANSWER 6 OF 14 PASCAL COPYRIGHT 2004 INIST-CNRS. ALL RIGHTS RESERVED. on STN DUPLICATE 2

ACCESSION NUMBER: 2004-0051791 PASCAL
COPYRIGHT NOTICE: Copyright .COPYRGT. 2004 INIST-CNRS. All rights reserved.
TITLE (IN ENGLISH): **HMG-CoA reductase inhibitor** increases GTP cyclohydrolase I mRNA and tetrahydrobiopterin in vascular endothelial cells
AUTHOR: HATTORI Yoshiyuki; NAKANISHI Nobuo; AKIMOTO Kazumi; YOSHIDA Mika; KASAI Kikuo
CORPORATE SOURCE: Department of Endocrinology and Metabolism, Dokkyo University School of Medicine, Mibu, Japan; Department of Biochemistry, Meikai University School of Dentistry Sakado, Saitama, Japan; Laboratory of Molecular and Cellular Biology, Dokkyo University School of Medicine, Mibu, Japan
SOURCE: Arteriosclerosis, thrombosis, and vascular biology, (2003), 23(2), 176-182, 40 refs.
ISSN: 1079-5642 CODEN: ATVBFA
DOCUMENT TYPE: Journal
BIBLIOGRAPHIC LEVEL: Analytic
COUNTRY: United States
LANGUAGE: English
AVAILABILITY: INIST-19104, 354000112574340070
ABSTRACT: Objective-Endothelial nitric oxide synthase (eNOS) activity is supported by tetrahydrobiopterin (BH4), which appears to be important for generating protective NO but decreases uncoupling formation of superoxide. We investigated the effects of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, or statins, in terms of BH4 metabolism in human umbilical vein endothelial cells (HUVECs). Methods and Results-We measured the mRNA levels of GTP cyclohydrolase I (GTPCH), the rate-limiting enzyme in the first step of de novo BH4 synthesis, by real-time polymerase chain reaction. The mRNA of GTPCH, as well as of eNOS, was upregulated in HUVECs treated with **cerivastatin**. This increase was time and dose dependent. **Fluvastatin** was also observed to enhance GTPCH and eNOS mRNA levels. In parallel with this observation, **cerivastatin** increased intracellular BH4. Incubating HUVECs with tumor necrosis factor (TNF-a) was observed to increase GTPCH mRNA while decreasing eNOS mRNA. In the presence of **cerivastatin**, the TNF-.alpha.-mediated increase in GTPCH mRNA was enhanced, and the TNF-.alpha.-mediated decrease in eNOS mRNA was attenuated. **Cerivastatin** increased the stability of eNOS mRNA. However, it did not alter the

stability of GTPCH mRNA but increased GTPCH gene transcription, as shown by nuclear run-on assays. Preteatment of HUVECs with the selective GTPCH inhibitor, 2,4-diamino-6-hydroxypyrimidine, caused a decrease in intracellular BH4 and decreased **citrulline** formation after stimulation with ionomycin. Furthermore, the potentiating effect of **cerivastatin** was decreased by limiting the cellular availability of BH4. Conclusions-Our data demonstrate that statins elevate GTPCH mRNA, thereby increasing BH4 levels in vascular endothelial cells. In addition to augmenting eNOS expression, statins potentiate GTPCH gene expression and BH4 synthesis, thereby increasing NO production and preventing relative shortages of BH4.

CLASSIFICATION CODE: 002B02N; Life sciences; Medical sciences; Pharmacology; Metabolic diseases

CONTROLLED TERM: Endothelial cell; Vascular wall; Tetrahydrobiopterin; GTP cyclohydrolase I; Umbilical vein; Human; **Cerivastatin**; Nitric-oxide synthase; Messenger RNA; Gene expression; Mechanism of action

BROADER TERM: Hydrolases; Enzyme; Oxidoreductases; Antilipemic agent; Enzyme inhibitor; Hydroxymethylglutaryl-CoA reductase; Statin derivative

L109 ANSWER 7 OF 14 PASCAL COPYRIGHT 2004 INIST-CNRS. ALL RIGHTS RESERVED. on STN DUPLICATE 3

ACCESSION NUMBER: 2002-0444560 PASCAL

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TITLE (IN ENGLISH): Rosuvastatin, a new **HMG-CoA reductase inhibitor**, upregulates endothelial nitric oxide synthase and protects from ischemic stroke in mice

AUTHOR: LAUFS Ulrich; GERTZ Karen; DIRNAGL Ulrich; BOEHM Michael; NICKENIG Georg; ENDRES Matthias

CORPORATE SOURCE: Medizinische Klinik und Poliklinik der Universitaet des Saarlandes, Innere Medizin III, 66421 Homburg, Germany, Federal Republic of; Klinik und Poliklinik fuer Neurologie, Charite, Humboldt-Universitaet zu Berlin, Schumannstr. 20/21, 10098 Berlin, Germany, Federal Republic of

SOURCE: Brain research, (2002), 942(1-2), 23-30, 30 refs. ISSN: 0006-8993 CODEN: BRREAP

DOCUMENT TYPE: Journal

BIBLIOGRAPHIC LEVEL: Analytic

COUNTRY: Netherlands

LANGUAGE: English

AVAILABILITY: INIST-12895, 354000101584760030

ABSTRACT: **HMG-CoA reductase inhibitors** (statins) are cholesterol-lowering drugs and reduce the risk of myocardial infarction and stroke. In this study we investigated whether rosuvastatin, a new, potent **HMG-CoA reductase inhibitor**, upregulates endothelial nitric oxide (NO) expression and activity and protects from cerebral ischaemia in mice. Endothelial cells in culture and 129/SV mice were chronically treated with rosuvastatin. The expression and activity of endothelial NO synthase (eNOS) was determined by reverse-transcriptase polymerase chain reaction (RT-PCR), Western blotting and arginine-

citrulline assays. Cerebral ischaemia was induced by occlusion of the middle cerebral artery (MCAo) for 2 h and infarct size was determined after 22 h of reperfusion. Treatment of endothelial cells with rosuvastatin concentration- and time-dependently upregulated eNOS mRNA and protein expression. In aortas of 129/SV wild-type mice, treatment with 0.2, 2, and 20 mg kg.sup.-.sup.1 rosuvastatin subcutaneously (s.c.) for 10 days significantly upregulated eNOS mRNA by 50, 142, and 205%, respectively. NOS activity was significantly increased by 75, 145, and 320%, respectively. Stroke volume after 2-h MCAo was reduced by 27, 56, and 50% (for 0.2, 2 and 20 mg kg respectively). Serum cholesterol and triglygeride levels were not significantly lowered by the treatment. The novel **HMG-CoA reductase inhibitor** rosuvastatin dose-dependently upregulates eNOS expression and activity and protects from cerebral ischaemia in mice. The effects are independent of changes in cholesterol levels and are equivalent or even superior to the protective effects by **simvastatin** and **atorvastatin** in this animal model.

CLASSIFICATION CODE: 002B02B10; Life sciences; Medical sciences; Pharmacology; Neurology, Nervous system

CONTROLLED TERM: Enzyme inhibitor; Reductase; Nitric-oxide synthase; Endothelium; Lipids; Metabolism; Stroke; Rosuvastatin; Ischemia; Neuroprotective agent; Brain (vertebrata); Experimental disease; Animal; Mouse

BROADER TERM: Oxidoreductases; Enzyme; Nervous system diseases; Central nervous system disease; Cerebral disorder; Cerebrovascular disease; Cardiovascular disease; Vascular disease; Rodentia; Mammalia; Vertebrata

L109 ANSWER 8 OF 14 on STN PASCAL COPYRIGHT 2004 INIST-CNRS. ALL RIGHTS RESERVED. DUPLICATE 4

ACCESSION NUMBER: 2002-0127683 PASCAL

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TITLE (IN ENGLISH): 3-Hydroxy-3-methylglutaryl coenzyme A reductase inhibitors upregulate inducible NO synthase expression and activity in vascular smooth muscle cells

AUTHOR: KOLYADA Alexey Y.; FEDTSOV Alexandre; MADIAS Nicolaos E.

CORPORATE SOURCE: Department of Medicine, Tufts University School of Medicine, and the Division of Nephrology and the Tupper Research Institute, New England Medical Center, Boston, Mass, United States

SOURCE: Hypertension : (Dallas, Tex. 1979), (2001), 38(5), 1024-1029, 24 refs.
ISSN: 0194-911X CODEN: HPRTDN

DOCUMENT TYPE: Journal

BIBLIOGRAPHIC LEVEL: Analytic

COUNTRY: United States

LANGUAGE: English

AVAILABILITY: INIST-18059, 354000094231620060

ABSTRACT: Inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase ameliorate atherosclerosis by both cholesterol-dependent and cholesterol-independent mechanisms. We examined whether **HMG-CoA reductase inhibitors** affect the expression and activity of inducible NO

synthase (iNOS) in cultured rat aortic vascular smooth muscle (VSM) cells. **Atorvastatin** (34 to 68 .mu.mol/L) markedly increased nitrite production, an increase that was essentially abrogated by the NO synthase inhibitor N.sup.G-monomethyl-L-arginine (500 .mu.mol/L). Activity of iNOS, determined by the conversion of L-arginine to L-**citrulline**, increased 9-fold after **atorvastatin** treatment. Western blot and semiquantitative reverse transcriptase-polymerase chain reaction revealed that **atorvastatin** (34 to 68 .mu.mol/L) strongly upregulated iNOS protein and mRNA levels, respectively. These concentrations of **atorvastatin** did not cause cytotoxicity, as judged by the cell survival rate. Similarly, **simvastatin** and **lovastatin** (34 .mu.mol/L) caused robust upregulation of the iNOS protein level. Transfection experiments demonstrated that the -1034- to 88-bp human iNOS promoter was strongly induced by **atorvastatin** (34 .mu.mol/L). Electromobility and supershift assays using a nuclear factor-KB (NF-KB) consensus oligonucleotide and nuclear extracts from VSM cells as well as transfection studies using an NF-KB reporter plasmid suggested that the transcriptional activation of the iNOS gene by **atorvastatin** is not mediated via the NF-KB pathway. We conclude that **HMG-CoA reductase inhibitors** potently upregulate iNOS expression and activity in VSM cells, at least in part, by transcriptional mechanisms that do not depend on transcription factor NF-KB. These effects might have important implications for the impact of **HMG -CoA reductase inhibitors** on atherosclerosis.

CLASSIFICATION CODE: 002B02F09; Life sciences; Medical sciences; Pharmacology; Cardiovascular system

CONTROLLED TERM: Myocyte; Aorta; Vascular wall; Cell culture; Rat; Animal; Nitric oxide; Synthase; Enzyme inhibitor; Hydroxymethylglutaryl-CoA reductase; Gene expression; Enzymatic activity; Exploration; Pharmacologic test; Mechanism of action; Regulation(control); Transcription

BROADER TERM: Rodentia; Mammalia; Vertebrata; Enzyme; Oxidoreductases; Circulatory system; Blood vessel

L109 ANSWER 9 OF 14 PASCAL COPYRIGHT 2004 INIST-CNRS. ALL RIGHTS RESERVED.
on STN DUPLICATE 5

ACCESSION NUMBER: 1996-0345504 PASCAL

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TITLE (IN ENGLISH): Acute multiple sclerosis (Marburg type) is associated with developmentally immature myelin basic protein

AUTHOR: WOOD D. D.; BILBAO J. M.; O'CONNORS P.; MOSCARELLO M. A.

CORPORATE SOURCE: Division of Biochemistry, Research Institute, Hospital for Sick Children, Toronto, Ontario, Canada

SOURCE: Annals of neurology, (1996), 40(1), 18-24, 17 refs. ISSN: 0364-5134 CODEN: ANNED3

DOCUMENT TYPE: Journal

BIBLIOGRAPHIC LEVEL: Analytic

COUNTRY: United States

LANGUAGE: English
AVAILABILITY: INIST-16555, 354000060480200040
ABSTRACT: We have studied a case of acute, fulminating multiple sclerosis (MS) (Marburg type) at the pathological and biochemical levels. Postmortem examination of the brain revealed extensive areas of gross rarefaction in the hemispheric white matter. Histologically, well-demarcated areas of demyelination with a large influx of macrophages and a subtle perivascular infiltration of lymphocytes were seen with relative preservation of the axis cylinders. Myelin basic protein (MBP) was isolated and purifed from noninvolved white matter. It was slightly larger in molecular weight than MBP from normal brain or from chronic MS brain. The increase in mass was accounted for, in part, by the deimination of 18 of 19 arginyl residues to **citrulline**, making the patient's MBP much less cationic than MBP from normal white matter. When expressed as the ratio of least cationic form of MBP to the most cationic (C-8/C-1), the normal ratio was 0.82, chronic MS 2.5, and the patient in this study 6.7. Because the ratio of 6.7 was similar to 7.5 found for a 15-month-old infant, MBP was considered to be of the immature form. The data are consistent with a genetic factor influencing the charge microheterogeneity of MBP. The resulting less cationic MBP cannot carry out its normal function of **compacting** multilayers.
CLASSIFICATION CODE: 002B17F; Life sciences; Medical sciences; Neurology, Nervous system
CONTROLLED TERM: Multiple sclerosis; Acute; Basic protein; Myelin; Developmental disorder; Case study; Pathogenesis; Adult
BROADER TERM: Human; Nervous system diseases; Central nervous system disease; Inflammatory disease

L109 ANSWER 10 OF 14 PASCAL COPYRIGHT 2004 INIST-CNRS. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 2000-0389245 PASCAL
COPYRIGHT NOTICE: Copyright .COPYRGT. 2000 INIST-CNRS. All rights reserved.
TITLE (IN ENGLISH): Inhibition of Rho protein stimulates iNOS expression in rat vascular smooth muscle cells
AUTHOR: MUNIYAPPA R.; RUI XU; RAM J. L.; SOWERS J. R.
CORPORATE SOURCE: Department of Physiology, Wayne State University School of Medicine, Detroit, Michigan 48201, United States; Department of Medicine and Cell Biology, State University of New York Health Sciences Center and Veterans Affairs New York Harbor Healthcare Center, Brooklyn, New York 11203, United States
SOURCE: American journal of physiology. Heart and circulatory physiology, (2000), 47(6), H1762-H1768, 49 refs. ISSN: 0363-6135 CODEN: AJPPDI
DOCUMENT TYPE: Journal
BIBLIOGRAPHIC LEVEL: Analytic
COUNTRY: United States
LANGUAGE: English
AVAILABILITY: INIST-670D, 354000088882090040
ABSTRACT: Inducible nitric oxide synthase (iNOS) in vascular smooth muscle cells (VSMCs) is upregulated in arterial injury and plays a role in regulating VSMC proliferation and restenosis. Inflammatory cytokines

[e.g., interleukin-1.beta. (IL-1.beta.)] released during vascular injury induce iNOS. Small GTP-binding proteins of the Ras superfamily play a major role in IL-1.beta.-dependent signaling pathways. In this study, we examined the role of Rho GTPases in regulating iNOS expression in VSMCs. Treatment of VSMCs with **mevastatin**, which inhibits isoprenylation of Rho and other small GTP-binding proteins, produced significantly higher amounts of IL-1.beta.-evoked NO and iNOS protein compared with control. Similarly, bacterial toxins [Toxin B from Clostridium difficile and C3 ADP-ribosyl transferase (C3) toxin from Clostridium botulinium] that specifically inactivate Rho proteins increased NOS products (NO and **citrulline**) and iNOS expression. Toxin B increased the activity of iNOS promoter-reporter construct in VSMCs. Both toxins enhanced IL-1.beta.-stimulated iNOS expression and NO production. These data demonstrate for the first time that inhibition of Rho induces iNOS and suggest a role for Rho protein in IL-1.beta.-stimulated NO production in VSMCs.

CLASSIFICATION CODE: 002A22D; Life sciences; Biological sciences; Vertebrates physiology, Cardiovascular system

CONTROLLED TERM: Protein inhibitor; Gene expression; Molecular form; Nitric-oxide synthase; Thoracic aorta; Smooth muscle; Stimulation; Guanosine-5'-triphosphate3'-diphosphate pyrophosphatase; Rat; Animal

BROADER TERM: Oxidoreductases; Enzyme; Hydrolases; Artery; Blood vessel; Circulatory system; Rodentia; Mammalia; Vertebrata

L109 ANSWER 11 OF 14 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN

ACCESSION NUMBER: 2003:219160 BIOSIS

DOCUMENT NUMBER: PREV200300219160

TITLE: Acute reduction of myocardial infarct size by a **HMG -CoA reductase inhibitor** is mediated by endothelial nitric oxide synthase.

AUTHOR(S): Wolfrum, S. [Reprint Author]; Grimm, M.; Heidbreder, M.; Dendorfer, A.; Katus, H. A. [Reprint Author]; Liao, J. K.; Richardt, G. [Reprint Author]

CORPORATE SOURCE: Medical Clinic II, University of Luebeck, Luebeck, Germany

SOURCE: European Heart Journal, (August-September 2002) Vol. 23, No. Abstract Supplement, pp. 214. print.
Meeting Info.: Congress of the European Society of Cardiology. Berlin, Germany. August 31-September 04, 2002. European Society of Cardiology.
ISSN: 0195-668X (ISSN print).

DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)

LANGUAGE: English

ENTRY DATE: Entered STN: 7 May 2003
Last Updated on STN: 7 May 2003

CONCEPT CODE: General biology - Symposia, transactions and proceedings 00520
Biochemistry studies - Proteins, peptides and amino acids 10064
Biochemistry studies - Sterols and steroids 10067
Enzymes - General and comparative studies: coenzymes 10802
Pathology - Therapy 12512

Cardiovascular system - Physiology and biochemistry 14504
Cardiovascular system - Heart pathology 14506
Cardiovascular system - Blood vessel pathology 14508
Blood - Blood and lymph studies 15002
Blood - Blood cell studies 15004
Muscle - Physiology and biochemistry 17504
Pharmacology - General 22002
Pharmacology - Cardiovascular system 22010

INDEX TERMS: Major Concepts
Cardiovascular System (Transport and Circulation); Enzymology (Biochemistry and Molecular Biophysics); Pharmacology

INDEX TERMS: Parts, Structures, & Systems of Organisms
heart: circulatory system; myocardium: circulatory system, muscular system; plasma: blood and lymphatics

INDEX TERMS: Diseases
ischemia/reperfusion injury: vascular disease
Reperfusion Injury (MeSH)

INDEX TERMS: Diseases
ischemic injury: vascular disease
Ischemia (MeSH)

INDEX TERMS: Diseases
myocardial infarction: heart disease, vascular disease
Myocardial Infarction (MeSH)

INDEX TERMS: Chemicals & Biochemicals
L-NAME: enzyme inhibitor-drug; **cerivastatin**: **HMG CoA reductase inhibitor**-drug, cardiovascular-drug, enzyme inhibitor-drug; cholesterol; endothelial nitric oxide synthase [eNOS] [EC 1.14.13.39]; statins: **HMG CoA reductase inhibitor** -drug, cardiovascular-drug, enzyme inhibitor-drug

INDEX TERMS: Methods & Equipment
TTC staining: laboratory techniques; arginine to **citrulline** conversion assay: laboratory techniques; coronary artery occlusion: experimental surgical techniques, laboratory techniques; reperfusion: laboratory techniques

INDEX TERMS: Miscellaneous Descriptors
arterial blood pressure; cardioprotection; heart rate; hemodynamics; infarct size

ORGANISM: Classifier
Muridae 86375
Super Taxa
Rodentia; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
rat (common)
Taxa Notes
Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Rodents, Vertebrates

REGISTRY NUMBER: 50903-99-6 (L-NAME)
145599-86-6 (**cerivastatin**)
57-88-5 (cholesterol)
503473-02-7 (endothelial nitric oxide synthase)
125978-95-2 (endothelial nitric oxide synthase)
503473-02-7 (eNOS)
125978-95-2 (eNOS)
503473-02-7 (EC 1.14.13.39)
125978-95-2 (EC 1.14.13.39)
148-79-8Q (statins)
79902-63-9Q (statins)

L109 ANSWER 12 OF 14 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN
ACCESSION NUMBER: 2000:358177 BIOSIS
DOCUMENT NUMBER: PREV200000358177
TITLE: Inhibition of Rho protein stimulates iNOS expression in rat vascular smooth muscle cells.
AUTHOR(S): Muniyappa, Ranganath; Xu, Rui; Ram, Jeffrey L.; Sowers, James R. [Reprint author]
CORPORATE SOURCE: SUNY Health Science Center, 450 Clarkson Ave., Brooklyn, NY, 11203, USA
SOURCE: American Journal of Physiology, (June, 2000) Vol. 278, No. 6 Part 2, pp. H1762-H1768. print.
CODEN: AJPHAP. ISSN: 0002-9513.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 16 Aug 2000
Last Updated on STN: 8 Jan 2002
ABSTRACT:Inducible nitric oxide synthase (iNOS) in vascular smooth muscle cells (VSMCs) is upregulated in arterial injury and plays a role in regulating VSMC proliferation and restenosis. Inflammatory cytokines (e.g., interleukin-1beta (IL-1beta)) released during vascular injury induce iNOS. Small GTP-binding proteins of the Ras superfamily play a major role in IL-1beta-dependent signaling pathways. In this study, we examined the role of Rho GTPases in regulating iNOS expression in VSMCs. Treatment of VSMCs with ***mevastatin*** , which inhibits isoprenylation of Rho and other small GTP-binding proteins, produced significantly higher amounts of IL-1beta-evoked NO and iNOS protein compared with control. Similarly, bacterial toxins (Toxin B from Clostridium difficile and C3 ADP-ribosyl transferase (C3) toxin from Clostridium botulinium) that specifically inactivate Rho proteins increased NOS products (NO and **citrulline**) and iNOS expression. Toxin B increased the activity of iNOS promoter-reporter construct in VSMCs. Both toxins enhanced IL-1beta-stimulated iNOS expression and NO production. These data demonstrate for the first time that inhibition of Rho induces iNOS and suggest a role for Rho protein in IL-1beta-stimulated NO production in VSMCs.
CONCEPT CODE:
Cytology - Animal 02506
Cytology - General 02502
Biochemistry studies - General 10060
Biochemistry studies - Proteins, peptides and amino acids 10064
Enzymes - General and comparative studies: coenzymes 10802
Cardiovascular system - Physiology and biochemistry 14504
Cardiovascular system - Blood vessel pathology 14508
Muscle - Physiology and biochemistry 17504
INDEX TERMS:
Major Concepts
Enzymology (Biochemistry and Molecular Biophysics); Cell Biology; Cardiovascular System (Transport and Circulation)
INDEX TERMS:
Parts, Structures, & Systems of Organisms
vascular smooth muscle cells: circulatory system, muscular system
INDEX TERMS:
Diseases
vascular injury: vascular disease
INDEX TERMS:
Chemicals & Biochemicals
Rho; inducible nitric oxide synthase [iNOS]; interleukin-1beta; nitric oxide [NO]
ORGANISM:
Classifier
Muridae 86375
Super Taxa
Rodentia; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
rat

Taxa Notes
Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Rodents, Vertebrates
REGISTRY NUMBER: 10102-43-9 (nitric oxide)
10102-43-9 (NO)

L109 ANSWER 13 OF 14 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 2000190190 EMBASE
TITLE: Inborn errors of metabolism and pregnancy.
AUTHOR: Walter J.H.
CORPORATE SOURCE: J.H. Walter, Willink Biochemical Genetics Unit, Royal Manchester Children's Hospital, Manchester M27 4HA, United Kingdom. john@jhwalter.demon.co.uk
SOURCE: Journal of Inherited Metabolic Disease, (2000) 23/3 (229-236).
Refs: 40
ISSN: 0141-8955 CODEN: JIMDDP
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 003 Endocrinology
007 Pediatrics and Pediatric Surgery
010 Obstetrics and Gynecology
022 Human Genetics
029 Clinical Biochemistry
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ABSTRACT:
An increasing number of women with inborn errors of metabolism are now reaching child-bearing age. For certain disorders there are maternal risks associated with pregnancy. These may be related to an increased likelihood of metabolic decompensation (e.g. disorders of the urea cycle) or to increased stress to systems already compromised by disease (e.g. cardiomyopathy in GSD III). Detrimental effects upon the fetus may also be caused by maternal disease, as occurs with phenylketonuria, or from medication used to treat the mother's condition. Less commonly, fetal inborn errors may adversely effect the mother's health - e.g. fetal long-chain acyl-CoA dehydrogenase deficiency and the maternal HELLP syndrome (haemolysis, elevated liver enzymes and low platelets) and AFLP (acute fatty liver of pregnancy). Because of the rarity of individual disorders, our knowledge of risks associated with pregnancy is limited. Even for more common inborn errors such as phenylketonuria, there remain a number of questions that have not been fully answered.

CONTROLLED TERM: Medical Descriptors:
*inborn error of metabolism: CN, congenital disorder
*inborn error of metabolism: DT, drug therapy
*inborn error of metabolism: ET, etiology
*pregnancy
HELLP syndrome: ET, etiology
cardiomyopathy: ET, etiology
drug safety
enzyme deficiency: ET, etiology
fatty liver: ET, etiology
fetus disease: ET, etiology
maternal disease: ET, etiology
phenylketonuria: ET, etiology
prenatal drug exposure
risk
stress
survival
urea cycle

human
conference paper
Drug Descriptors:
5 hydroxytryptophan: DT, drug therapy
acyl coenzyme A dehydrogenase: EC, endogenous compound
alpha tocopherol: DT, drug therapy
arginine: DT, drug therapy
betaine: DT, drug therapy
biotin: DT, drug therapy
carnitine: DT, drug therapy
chenodeoxycholic acid: DT, drug therapy
cholesterol: DT, drug therapy
citrulline: DT, drug therapy
colestyramine: DT, drug therapy
cystafos: DT, drug therapy
dextromethorphan: DT, drug therapy
dichloroacetic acid: DT, drug therapy
folinic acid: DT, drug therapy
glycine: DT, drug therapy
hydroxocobalamin: DT, drug therapy
hydroxymethylglutaryl coenzyme A reductase inhibitor: DT, drug therapy
imiglucerase: DT, drug therapy
ketamine: DT, drug therapy
levodopa: DT, drug therapy
mercaptamine: DT, drug therapy
metronidazole: DT, drug therapy
penicillamine: DT, drug therapy
pyridoxine: DT, drug therapy
riboflavin: DT, drug therapy
tetrathiomolybdate ammonium: DT, drug therapy
trientine: DT, drug therapy
unindexed drug: DT, drug therapy
ursodeoxycholic acid: DT, drug therapy

CAS REGISTRY NO.: (5 hydroxytryptophan) 4350-09-8, 56-69-9; (acyl coenzyme A dehydrogenase) 9027-65-0; (alpha tocopherol) 1406-18-4, 1406-70-8, 52225-20-4, 58-95-7, 59-02-9; (arginine) 1119-34-2, 15595-35-4, 7004-12-8, 74-79-3; (betaine) 107-43-7, 590-46-5; (biotin) 58-85-5; (carnitine) 461-06-3, 541-15-1, 56-99-5; (chenodeoxycholic acid) 474-25-9; (cholesterol) 57-88-5; (citrulline) 372-75-8; (colestyramine) 11041-12-6, 58391-37-0; (cystafos) 3724-89-8; (dextromethorphan) 125-69-9, 125-71-3; (dichloroacetic acid) 13425-80-4, 2156-56-1, 79-43-6; (folinic acid) 58-05-9, 68538-85-2; (glycine) 56-40-6, 6000-43-7, 6000-44-8; (hydroxocobalamin) 13422-51-0, 13422-52-1; (imiglucerase) 154248-97-2; (ketamine) 1867-66-9, 6740-88-1, 81771-21-3; (levodopa) 59-92-7; (mercaptamine) 156-57-0, 60-23-1; (metronidazole) 39322-38-8, 443-48-1; (penicillamine) 2219-30-9, 52-67-5; (pyridoxine) 12001-77-3, 58-56-0, 65-23-6, 8059-24-3; (riboflavin) 83-88-5; (tetrathiomolybdate ammonium) 15060-55-6; (trientine) 112-24-3, 38260-01-4; (ursodeoxycholic acid) 128-13-2, 2898-95-5

L109 ANSWER 14 OF 14 USPATFULL on STN
ACCESSION NUMBER: 2004:31915 USPATFULL
TITLE: Nitrosated nonsteroidal antiinflammatory compounds, compositions and methods of use related applications

INVENTOR(S): Earl, Richard A., Westford, MA, UNITED STATES
Ezawa, Maiko, Acton, MA, UNITED STATES
Fang, Xinqin, Lexington, MA, UNITED STATES
Garvey, David S., Dover, MA, UNITED STATES
Gaston, Ricky D., Malden, MA, UNITED STATES
Khanapure, Subhash P., Clinton, MA, UNITED STATES
Letts, L. Gordon, Dover, MA, UNITED STATES
Lin, Chia-En, Burlington, MA, UNITED STATES
Ranatunga, Ramani R., Lexington, MA, UNITED STATES
Richardson, Stewart K., Tolland, CT, UNITED STATES
Schroeder, Joseph D., Minneapolis, MN, UNITED STATES
Stevenson, Cheri A., Haverhill, MA, UNITED STATES
Wey, Shiow-Jyi, Woburn, MA, UNITED STATES
PATENT ASSIGNEE(S): NitroMed, Inc. (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2004024057	A1	20040205	
APPLICATION INFO.:	US 2003-612014	A1	20030703	(10)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2002-393111P	20020703 (60)
	US 2002-397979P	20020724 (60)
	US 2002-418353P	20021016 (60)
	US 2003-449798P	20030226 (60)
	US 2003-456182P	20030321 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: EDWARD D GRIEFF, HALE & DORR LLP, 1455 PENNSYLVANIA AVE, NW, WASHINGTON, DC, 20004
NUMBER OF CLAIMS: 58
EXEMPLARY CLAIM: 1
LINE COUNT: 5705
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The invention describes novel nitrosated nonsteroidal antiinflammatory drugs (NSAIDs) and pharmaceutically acceptable salts thereof, and novel compositions comprising at least one nitrosated NSAID, and, optionally, at least one compound that donates, transfers or releases nitric oxide, stimulates endogenous synthesis of nitric oxide, elevates endogenous levels of endothelium-derived relaxing factor or is a substrate for nitric oxide synthase, and/or at least one therapeutic agent. The invention also provides novel compositions comprising at least one nitrosated NSAID, and at least one compound that donates, transfers or releases nitric oxide, elevates endogenous levels of endothelium-derived relaxing factor, stimulates endogenous synthesis of nitric oxide or is a substrate for nitric oxide synthase and/or at least one therapeutic agent. The invention also provides novel kits comprising at least one nitrosated NSAID, and, optionally, at least one nitric oxide donor and/or at least one therapeutic agent. The invention also provides methods for treating inflammation, pain and fever; for treating gastrointestinal disorders; for facilitating wound healing; for treating and/or preventing gastrointestinal, renal and/or respiratory toxicities resulting from the use of nonsteroidal antiinflammatory compounds; for treating inflammatory disease states and/or disorders; and for treating and/or preventing ophthalmic diseases and/or disorders.

IT **372-75-8**, Citrulline
(combination pharmaceutical; prepn. of naproxen-derived nitrosated antiinflammatory compds.)

IT **9028-35-7**, 3-Hydroxy-3-methylglutaryl coenzyme A reductase
(**inhibitor**, combination pharmaceutical; prepn. of naproxen-derived nitrosated antiinflammatory compds.)

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=> fil capl; d que l27; d que l34
FILE 'CAPLUS' ENTERED AT 12:54:53 ON 23 SEP 2004
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FILE COVERS 1907 - 23 Sep 2004  VOL 141 ISS 13
FILE LAST UPDATED: 22 Sep 2004  (20040922/ED)

  This file contains CAS Registry Numbers for easy and accurate
  substance identification.

'OBI' IS DEFAULT SEARCH FIELD FOR 'CAPLUS' FILE


L3            1 SEA FILE=REGISTRY ABB=ON  CITRULLINE/CN
L4            1 SEA FILE=REGISTRY ABB=ON  L-CITRULLINE/CN
L5            1 SEA FILE=REGISTRY ABB=ON  "L-CITRULLINE HYDROCHLORIDE"/CN
L6            2 SEA FILE=REGISTRY ABB=ON  (L3 OR L4 OR L5)
L9            1 SEA FILE=REGISTRY ABB=ON  125978-95-2
L20        3622 SEA FILE=CAPLUS ABB=ON  L6
L24       19461 SEA FILE=CAPLUS ABB=ON  L9
L26          94 SEA FILE=CAPLUS ABB=ON  L24(L)AGONIST?/OBI
L27           3 SEA FILE=CAPLUS ABB=ON  L26 AND L20



L3            1 SEA FILE=REGISTRY ABB=ON  CITRULLINE/CN
L4            1 SEA FILE=REGISTRY ABB=ON  L-CITRULLINE/CN
L5            1 SEA FILE=REGISTRY ABB=ON  "L-CITRULLINE HYDROCHLORIDE"/CN
L6            2 SEA FILE=REGISTRY ABB=ON  (L3 OR L4 OR L5)
L9            1 SEA FILE=REGISTRY ABB=ON  125978-95-2
L20        3622 SEA FILE=CAPLUS ABB=ON  L6
L24       19461 SEA FILE=CAPLUS ABB=ON  L9
L26          94 SEA FILE=CAPLUS ABB=ON  L24(L)AGONIST?/OBI
L27           3 SEA FILE=CAPLUS ABB=ON  L26 AND L20
L28         220 SEA FILE=CAPLUS ABB=ON  L20(L)(BAC OR PAC OR PKT OR DMA OR
                THU)/RL
L29          49 SEA FILE=CAPLUS ABB=ON  L28 AND L24
L30         139 SEA FILE=CAPLUS ABB=ON  ((NITRIC OXIDE)(W)SYNTH?(5A)AGONI?)/BI

L31           2 SEA FILE=CAPLUS ABB=ON  L30 AND L28
L33          47 SEA FILE=CAPLUS ABB=ON  L29 NOT (L31 OR L27)
L34           3 SEA FILE=CAPLUS ABB=ON  L33 AND VASCULAR/TI


=> s l27 or l34

L110          6 L27 OR L34
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=> fil uspatf; d que l58

FILE 'USPATFULL' ENTERED AT 12:54:55 ON 23 SEP 2004
CA INDEXING COPYRIGHT (C) 2004 AMERICAN CHEMICAL SOCIETY (ACS)

FILE COVERS 1971 TO PATENT PUBLICATION DATE: 23 Sep 2004 (20040923/PD)
FILE LAST UPDATED: 23 Sep 2004 (20040923/ED)
HIGHEST GRANTED PATENT NUMBER: US6795973
HIGHEST APPLICATION PUBLICATION NUMBER: US2004187181
CA INDEXING IS CURRENT THROUGH 23 Sep 2004 (20040923/UPCA)
ISSUE CLASS FIELDS (/INCL) CURRENT THROUGH: 23 Sep 2004 (20040923/PD)
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Jun 2004
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Jun 2004

>>>  USPAT2 is now available.  USPATFULL contains full text of the     <<<
>>>  original, i.e., the earliest published granted patents or         <<<
>>>  applications.  USPAT2 contains full text of the latest US         <<<
>>>  publications, starting in 2001, for the inventions covered in     <<<
>>>  USPATFULL.  A USPATFULL record contains not only the original     <<<
>>>  published document but also a list of any subsequent              <<<
>>>  publications.  The publication number, patent kind code, and      <<<
>>>  publication date for all the US publications for an invention     <<<
>>>  are displayed in the PI (Patent Information) field of USPATFULL   <<<
>>>  records and may be searched in standard search fields, e.g., /PN, <<<
>>>  /PK, etc.                                                         <<<

>>>  USPATFULL and USPAT2 can be accessed and searched together        <<<
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>>>  Use USPATALL when searching terms such as patent assignees,       <<<
>>>  classifications, or claims, that may potentially change from      <<<
>>>  the earliest to the latest publication.                           <<<

This file contains CAS Registry Numbers for easy and accurate
substance identification.


L3            1 SEA FILE=REGISTRY ABB=ON  CITRULLINE/CN
L4            1 SEA FILE=REGISTRY ABB=ON  L-CITRULLINE/CN
L5            1 SEA FILE=REGISTRY ABB=ON  "L-CITRULLINE HYDROCHLORIDE"/CN
L6            2 SEA FILE=REGISTRY ABB=ON  (L3 OR L4 OR L5)
L9            1 SEA FILE=REGISTRY ABB=ON  125978-95-2
L41         181 SEA FILE=USPATFULL ABB=ON  L6
L47         740 SEA FILE=USPATFULL ABB=ON  L9
L49         744 SEA FILE=USPATFULL ABB=ON  ((NITRIC OXIDE OR ENDOTHELIUM
                DERIVED GROWTH FACTOR OR EDRF OR GUANYLYL CYCLASE ACTIVATING
                FACTOR)(W)SYNTH?)/IT
L50        3127 SEA FILE=USPATFULL ABB=ON  ((NITRIC OXIDE OR ENDOTHELIUM
                DERIVED GROWTH FACTOR OR EDRF OR GUANYLYL CYCLASE ACTIVATING
                FACTOR)(W)SYNTH?)
L54          19 SEA FILE=USPATFULL ABB=ON  CITRULLINE(5A)(FED OR FEED? OR
                ADMINIST?)
L56          72 SEA FILE=USPATFULL ABB=ON  (L49 OR L47)(L)(STIMULAT? OR AGONI?
                OR ACTIVAT?)/IT
L57         696 SEA FILE=USPATFULL ABB=ON  L50(3A)(STIMULAT? OR AGONI? OR
                ACTIVAT?)
L58           4 SEA FILE=USPATFULL ABB=ON  (L56 OR L57) AND L54 AND L41


=> fil medl; d que l74
```

FILE 'MEDLINE' ENTERED AT 12:54:55 ON 23 SEP 2004

FILE LAST UPDATED: 22 SEP 2004 (20040922/UP). FILE COVERS 1951 TO DATE.

On February 29, 2004, the 2004 MeSH terms were loaded. See HELP RLOAD for details. OLDMEDLINE now back to 1951.

MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the MeSH 2004 vocabulary. See http://www.nlm.nih.gov/mesh/ and http://www.nlm.nih.gov/pubs/techbull/nd03/nd03_mesh.html for a description of changes.

This file contains CAS Registry Numbers for easy and accurate substance identification.

L59	2100	SEA FILE=MEDLINE ABB=ON	CITRULLINE/CT
L64	23202	SEA FILE=MEDLINE ABB=ON	NITRIC-OXIDE SYNTHASE/CT
L65	274	SEA FILE=MEDLINE ABB=ON	L59(L)(AD OR PD OR PK OR TU)/CT
L72	3052	SEA FILE=MEDLINE ABB=ON	ENZYME ACTIVATORS+NT/CT
L73	66952	SEA FILE=MEDLINE ABB=ON	ENZYME ACTIVATION+NT/CT
L74	2	SEA FILE=MEDLINE ABB=ON	L65 AND L64 AND (L72 OR L73)

=> fil embase; d que l87; d que l94

FILE 'EMBASE' ENTERED AT 12:54:56 ON 23 SEP 2004
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FILE COVERS 1974 TO 16 Sep 2004 (20040916/ED)

EMBASE has been reloaded. Enter HELP RLOAD for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

L75	2121	SEA FILE=EMBASE ABB=ON	CITRULLINE/CT OR CITRULLINE DERIVATIVE/CT
L86	2	SEA FILE=EMBASE ABB=ON	NITRIC OXIDE SYNTHASE ACTIVATOR/CT OR NITRIC OXIDE SYNTHASE AGONIST/CT
L87	0	SEA FILE=EMBASE ABB=ON	L86 AND L75

L75	2121	SEA FILE=EMBASE ABB=ON	CITRULLINE/CT OR CITRULLINE DERIVATIVE/CT
L85	21844	SEA FILE=EMBASE ABB=ON	NITRIC OXIDE SYNTHASE/CT
L88	198457	SEA FILE=EMBASE ABB=ON	ENZYME INDUCTION/CT OR ENZYME ACTIVITY/CT
L89	53123	SEA FILE=EMBASE ABB=ON	ENZYME ACTIVATION/CT
L90	902	SEA FILE=EMBASE ABB=ON	ENZYME ACTIVATOR/CT
L91	384	SEA FILE=EMBASE ABB=ON	ENZYME INDUCING AGENT/CT
L93	103	SEA FILE=EMBASE ABB=ON	L75(L)(DT OR PD OR AD OR DO)/CT
L94	7	SEA FILE=EMBASE ABB=ON	L93 AND L85 AND (L88 OR L89 OR L90 OR L91)

=> fil DRUGU, PASCAL, BIOSIS, WPIDS; d que l108

FILE 'DRUGU' ENTERED AT 12:54:57 ON 23 SEP 2004
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FILE 'PASCAL' ENTERED AT 12:54:57 ON 23 SEP 2004

FILE 'BIOSIS' ENTERED AT 12:54:57 ON 23 SEP 2004

FILE 'WPIDS' ENTERED AT 12:54:57 ON 23 SEP 2004

L95 6253 SEA CITRULLINE OR NSC27425 OR NSC 27425
L99 60838 SEA (NITRIC OXIDE OR ENDOTHELIUM DERIVED GROWTH FACTOR OR EDRF OR GUANYLYL CYCLASE ACTIVATING FACTOR)(W) SYNTH?
L102 53 SEA L95(5A)(FED OR FEED? OR ADMIN?)
L107 434831 SEA DEFICIEN?
L108 1 SEA L102 AND L107 AND L99

=> dup rem l74,l110,l108,l94,l58

FILE 'MEDLINE' ENTERED AT 12:54:58 ON 23 SEP 2004

FILE 'CAPLUS' ENTERED AT 12:54:58 ON 23 SEP 2004

FILE 'WPIDS' ENTERED AT 12:54:58 ON 23 SEP 2004

FILE 'EMBASE' ENTERED AT 12:54:58 ON 23 SEP 2004

FILE 'USPATFULL' ENTERED AT 12:54:58 ON 23 SEP 2004

PROCESSING COMPLETED FOR L74
PROCESSING COMPLETED FOR L110
PROCESSING COMPLETED FOR L108
PROCESSING COMPLETED FOR L94
PROCESSING COMPLETED FOR L58
L111 18 DUP REM L74 L110 L108 L94 L58 (2 DUPLICATES REMOVED)
ANSWERS '1-2' FROM FILE MEDLINE
ANSWERS '3-8' FROM FILE CAPLUS
ANSWER '9' FROM FILE WPIDS
ANSWERS '10-16' FROM FILE EMBASE
ANSWERS '17-18' FROM FILE USPATFULL

=> d iall 1-2; d ibib ed ab hitrn 3-8; d iall 9-16; d ibib ab hitrn 17-18; fil hom

L111 ANSWER 1 OF 18 MEDLINE on STN
ACCESSION NUMBER: 2001564932 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11668066
TITLE: Comparison of neuronal and endothelial isoforms of nitric oxide synthase in stably transfected HEK 293 cells.
COMMENT: Erratum in: Am J Physiol Heart Circ Physiol 2002 Feb;282(2):following Table of Content
AUTHOR: Schmidt K; Andrew P; Schrammel A; Groschner K; Schmitz V; Kojda G; Mayer B

CORPORATE SOURCE: Institut fur Pharmakologie und Toxikologi, Karl-Franzens-Universitat, A-8010 Graz, Austria.
SOURCE: American journal of physiology. Heart and circulatory physiology, (2001 Nov) 281 (5) H2053-61. Journal code: 100901228. ISSN: 0363-6135.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200112
ENTRY DATE: Entered STN: 20011023
Last Updated on STN: 20020223
Entered Medline: 20011205

ABSTRACT:
The neuronal and endothelial isoforms of nitric oxide (NO) synthase (nNOS and eNOS, respectively) both catalyze the production of NO but are regulated differently. Stably transfected HEK 293 cell lines containing nNOS, eNOS, and a soluble mutant of eNOS were therefore established to compare their activity in a common cellular environment. NOS activity was determined by measuring L-[3H]citrulline production in homogenates and intact cells, the conversion of oxyhemoglobin to methemoglobin, and the production of cGMP. The results indicate that nNOS is more active than eNOS, both in unstimulated as well as calcium-stimulated cells. Under basal conditions, the soluble mutant of eNOS appeared to be slightly more active than wild-type eNOS in terms of NO and cGMP formation, suggesting that membrane association may be crucial for inhibition of basal NO release but is not required for stimulation by Ca2+-mobilizing agents. The maximal activity of soluble guanylate cyclase was significantly reduced by transfection with wild-type eNOS due to downregulation of mRNA expression. These results demonstrate that nNOS and eNOS behave differently even in an identical cellular environment.

CONTROLLED TERM: Check Tags: Comparative Study; Human; Support, Non-U.S. Gov't
Calcium Chloride: PD, pharmacology
Cell Line
Citrulline: PK, pharmacokinetics
Cyclic GMP: ME, metabolism
Enzyme Activation: DE, drug effects
Enzyme Activation: PH, physiology
Enzyme Inhibitors: PD, pharmacology
Gene Expression Regulation, Enzymologic
Guanylate Cyclase: ME, metabolism
Ionomycin: PD, pharmacology
Ionophores: PD, pharmacology
Kidney: CY, cytology
***Nitric-Oxide Synthase: GE, genetics**
***Nitric-Oxide Synthase: ME, metabolism**
Solubility
Thapsigargin: PD, pharmacology
Transfection
Tritium: DU, diagnostic use

CAS REGISTRY NO.: 10028-17-8 (Tritium); 10043-52-4 (Calcium Chloride); 372-75-8 (Citrulline); 56092-81-0 (Ionomycin); 67526-95-8 (Thapsigargin); 7665-99-8 (Cyclic GMP)
CHEMICAL NAME: 0 (Enzyme Inhibitors); 0 (Ionophores); EC 1.14.13.- (endothelial constitutive nitric oxide synthase); EC 1.14.13.- (neural constitutive nitric oxide synthase); EC 1.14.13.39 (Nitric-Oxide Synthase); EC 4.6.1.2 (Guanylate Cyclase)

L111 ANSWER 2 OF 18 MEDLINE on STN
ACCESSION NUMBER: 2000237765 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10773029

TITLE: Neurokinin(3) receptors couple to the activation of neuronal nitric-oxide synthase in stably transfected Chinese hamster ovary cells.
AUTHOR: Linden D R; Chell M J; El-Fakahany E E; Seybold V S
CORPORATE SOURCE: Department of Neuroscience, University of Minnesota, Minneapolis, Minnesota 55455, USA.
CONTRACT NUMBER: NS17702 (NINDS)
NS25743 (NINDS)
T32-DA07234 (NIDA)
SOURCE: Journal of pharmacology and experimental therapeutics, (2000 May) 293 (2) 559-68.
Journal code: 0376362. ISSN: 0022-3565.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200006
ENTRY DATE: Entered STN: 20000629
Last Updated on STN: 20000629
Entered Medline: 20000621

ABSTRACT:
Several physiological effects induced by activation of neurokinin(3) (NK(3)) receptors are mediated by the production of nitric oxide (NO). We investigated the intracellular coupling of NK(3) receptors to NO synthase (NOS) using a Chinese hamster ovary cell line that was stably transfected with both the NK(3) receptor and type I (neuronal) NOS. NOS activity in the transfected cell line was assayed directly, by measuring the formation of L-citrulline, another product of NOS, as well as indirectly, by measuring the production of cGMP in cultured rat fetal lung fibroblasts (RFL-6 cells). MePhe(7)-neurokinin B (NKB) stimulation of L-[(3)H]citrulline production was concentration-dependent and yielded a two-site model for the concentration-response relationship. The production of L-citrulline in response to two other tachykinins, substance P or neurokinin A, revealed only a one-site nature of the response. The production of cGMP in response to MePhe(7)-NKB had an EC(50) value that corresponded to the high-potency component of MePhe(7)-NKB-induced production of L-[(3)H]citrulline. Agonist-induced calcium signaling was also concentration-dependent, and the acute increase in the production of cGMP by MePhe(7)-NKB (0.1 nM) was dependent on the release of calcium from intracellular stores. Results of this study provide the first direct evidence that NK(3) receptors couple to the generation of NO within the same cell.
CONTROLLED TERM: Check Tags: Human; Support, U.S. Gov't, P.H.S.
Animals
CHO Cells
Calcium: ME, metabolism
Calcium Signaling: DE, drug effects
Cell Line
Citrulline: PD, pharmacology
Cyclic GMP: BI, biosynthesis
Enzyme Activation: DE, drug effects
Guanylate Cyclase: ME, metabolism
Hamsters
Immunohistochemistry
Inositol Phosphates: ME, metabolism
Neurokinin B: AA, analogs & derivatives
Neurokinin B: PD, pharmacology
Neurons: DE, drug effects
*Neurons: EN, enzymology
***Nitric-Oxide Synthase: ME, metabolism**
Piperidines: PD, pharmacology
Rats
Receptors, Neurokinin-3: DE, drug effects
*Receptors, Neurokinin-3: ME, metabolism

Transfection: GE, genetics
CAS REGISTRY NO.: 372-75-8 (Citrulline); 7440-70-2 (Calcium); 7665-99-8 (Cyclic GMP); 86933-75-7 (Neurokinin B)
CHEMICAL NAME: 0 (Inositol Phosphates); 0 (Piperidines); 0 (Receptors, Neurokinin-3); 0 (SR 142801); 0 (neurokinin B, MePhe(7)-); EC 1.14.13.- (neural constitutive nitric oxide synthase); EC 1.14.13.39 (Nitric-Oxide Synthase); EC 4.6.1.2 (Guanylate Cyclase)

L111 ANSWER 3 OF 18 CAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 2
ACCESSION NUMBER: 1998:435716 CAPLUS
DOCUMENT NUMBER: 129:62971
TITLE: Method and formulation of stimulating nitric oxide synthesis
INVENTOR(S): Kaesemeyer, W. H.
PATENT ASSIGNEE(S): Notol, Inc., USA
SOURCE: U.S., 18 pp., Cont.-in-part of U.S. 5,543,430. CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 7
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5767160	A	19980616	US 1996-693882	19960805
US 5543430	A	19960806	US 1994-321051	19941005
CA 2201784	AA	19960418	CA 1995-2201784	19951005
CA 2201784	C	20040824		
US 5968983	A	19991019	US 1997-833842	19970410
PRIORITY APPLN. INFO.:			US 1994-321051	A2 19941005
			US 1996-693882	A2 19960805

ED Entered STN: 15 Jul 1998
AB A therapeutic in vitro or in vivo mixt. comprising L-arginine and an agonist of nitric oxide synthase, namely nitroglycerin is disclosed for the treatment of diseases related to vasoconstriction, wherein the vasoconstriction is relieved by stimulating the constitutive form of nitric oxide synthase (cNOS) to produce native nitric oxide (NO). The native NO having superior beneficial effect when compared to exogenous NO produced by an L-arginine independent pathway in terms of the ability to reduce clin. endpoints and mortality.
IT **125978-95-2**, Nitric oxide synthase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**agonists**; method and formulation of stimulating nitric oxide synthesis)
IT **372-75-8**, Citrulline
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(method and formulation of stimulating nitric oxide synthesis)
REFERENCE COUNT: 104 THERE ARE 104 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L111 ANSWER 4 OF 18 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2004:451474 CAPLUS
DOCUMENT NUMBER: 141:1258
TITLE: Nitrosated compounds in methods of treating **vascular** diseases characterized by nitric

oxide insufficiency
INVENTOR(S): Loscalzo, Joseph; Vita, Joseph A.; Loberg, Michael D.; Worcel, Manuel
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 23 pp., Cont.-in-part of U.S. Ser. No. 679,257.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 5
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
US 2004105850	A1	20040603	US 2003-692724		20031027
US 6635273	B1	20031021	US 2000-697317		20001027
US 2004071766	A1	20040415	US 2003-679257		20031007
PRIORITY APPLN. INFO.:			US 1999-162230P	P	19991029
			US 2000-179020P	P	20000131
			US 2000-697317	A1	20001027
			US 2003-679257	A2	20031007

OTHER SOURCE(S): MARPAT 141:1258
ED Entered STN: 04 Jun 2004
AB The invention provides methods of treating and/or preventing vascular diseases characterized by nitric oxide insufficiency by administering a therapeutically effective amt. of at least one nitrosated angiotensin-converting enzyme inhibitor, nitrosated beta-adrenergic blocker, nitrosated cholesterol reducer, nitrosated calcium channel blocker, nitrosated endothelin antagonist, nitrosated angiotensin II receptor antagonist, nitrosated renin inhibitor, and optionally at least one compd. used to treat cardiovascular diseases and/or at least one antioxidant, or a pharmaceutically acceptable salt thereof, and/or at least one compd. that donates, transfers or releases nitric oxide, elevates endogenous levels of endothelium-derived relaxing factor, stimulates endogenous synthesis of nitric oxide or is a substrate for nitric oxide synthase. The antioxidant may preferably be a hydralazine compd. or a pharmaceutically acceptable salt thereof. The compd. that donates, transfers or releases nitric oxide, elevates endogenous levels of endothelium-derived relaxing factor, stimulates endogenous synthesis of nitric oxide or is a substrate for nitric oxide synthase may preferably be isosorbide dinitrate and/or isosorbide mononitrate. The vascular diseases characterized by nitric oxide insufficiency include a cardiovascular disease and a disease resulting from oxidative stress. Nitric oxide action was shown to be impaired in the microvasculature of black hypertensive patients to a greater extent than in white hypertensive patients.
IT **372-75-8**, L-Citrulline
RL: BSU (Biological study, unclassified); **PAC (Pharmacological activity)**; **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(as further therapeutic agent; nitrosated compds. in methods of treating vascular diseases characterized by nitric oxide insufficiency)
IT **125978-95-2**, Nitric oxide synthase
RL: BSU (Biological study, unclassified); CAT (Catalyst use); BIOL (Biological study); USES (Uses)
(substrates for, as further therapeutic agents; nitrosated compds. in methods of treating vascular diseases characterized by nitric oxide insufficiency)

L111 ANSWER 5 OF 18 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2004:352951 CAPLUS
DOCUMENT NUMBER: 140:350582

TITLE: Methods and combination compositions using antioxidants, nitrosated compounds, and other agents for the treatment of **vascular** diseases characterized by nitric oxide insufficiency
INVENTOR(S): Loscalzo, Joseph; Vita, Joseph A.; Loberg, Michael D.; Worcel, Manuel
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 28 pp., Cont.-in-part of U.S. 6,635,273.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 5
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
US 2004081642	A1	20040429	US 2003-687706		20031020
US 6635273	B1	20031021	US 2000-697317		20001027
PRIORITY APPLN. INFO.:			US 1999-162230P	P	19991029
			US 2000-179020P	P	20000131
			US 2000-697317	A2	20001027

OTHER SOURCE(S): MARPAT 140:350582
ED Entered STN: 30 Apr 2004
AB The invention provides methods of treating or preventing vascular diseases caused by nitric oxide (NO) insufficiency. The methods encompass administering a compn. comprising an antioxidant, a compd. to treat cardiovascular diseases, a nitrosated compd., a compd. that donates, transfers or releases NO, or is a NO synthase substrate, or endogenously stimulates NO synthesis, or stimulates levels of endothelium derived relaxing factor. In the compn., a hydralazine compd. may be an antioxidant, isosorbide mono-or dinitrate may be the compd. to donate, transfer, release, or stimulate endogenous NO synthesis. The isosorbide may also elevate endogenous levels of endothelium-derived relaxing factor, or be a NO synthase substrate and angiotensin enzyme inhibitor may be nitrosated compd. Disclosed in the invention is also a method to treat, or prevent Renaud's syndrome by administering a therapeutically effective amt. of an antioxidant, a NO donor, a nitrosated compd. and novel sustained-release formulations (e.g. a transdermal patch).
IT **125978-95-2**, Nitric oxide synthase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(antioxidants, nitrosated compds., and other agents for treatment of vascular diseases characterized by nitric oxide insufficiency)
IT **372-75-8**, Citrulline
RL: **PAC (Pharmacological activity)**; **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(antioxidants, nitrosated compds., and other agents for treatment of vascular diseases characterized by nitric oxide insufficiency)

L111 ANSWER 6 OF 18 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:332068 CAPLUS
DOCUMENT NUMBER: 136:335235
TITLE: Methods of treating **vascular** diseases characterized by nitric oxide insufficiency
INVENTOR(S): Loscalzo, Joseph; Vita, Joseph A.; Loberg, Michael D.; Worcel, Manuel
PATENT ASSIGNEE(S): Nitromed, Inc., USA; Trustees of Boston University
SOURCE: PCT Int. Appl., 64 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 5

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002034303	A1	20020502	WO 2001-US14245	20010502
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
WO 2001035961	A1	20010525	WO 2000-US29528	20001027
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 6635273	B1	20031021	US 2000-697317	20001027
AU 2001059399	A5	20020506	AU 2001-59399	20010502
EP 1337283	A1	20030827	EP 2001-932915	20010502
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP 2004521083	T2	20040715	JP 2002-537354	20010502

PRIORITY APPLN. INFO.:	US 2000-697317	A	20001027
	WO 2000-US29528	W	20001027
	US 1999-162230P	P	19991029
	US 2000-179020P	P	20000131
	WO 2000-US29582	A	20001027
	WO 2001-US14245	W	20010502

OTHER SOURCE(S): MARPAT 136:335235

ED Entered STN: 03 May 2002

AB The present invention provides methods of treating or preventing vascular diseases caused by nitric oxide (NO) insufficiency. The methods encompass administering a compn. comprising an antioxidant, a compd. to treat cardiovascular diseases, a nitrosated compd., a compd. that donates, transfers or releases NO, or is a NO synthase substrate, or endogenously stimulates NO synthesis, or stimulates levels of endothelium derived relaxing factor. In the said compn., a hydralazine compd. may be an antioxidant, isosorbide mono-or dinitrate may be the compd. to donate, transfer, release, or stimulate endogenous NO synthesis. The isosorbide may also elevate endogenous levels of endothelium-derived relaxing factor, or be a NO synthase substrate and angiotensin enzyme inhibitor may be nitrosated compd. Disclosed in the invention is also a method to treat, or prevent Reynaud's syndrome by administering a therapeutically effective amt. of an antioxidant, a NO donor, a nitrosated compd. and novel sustained-release formulations (e.g. a transdermal patch).

IT **372-75-8**, Citrulline
RL: **PAC (Pharmacological activity)**; **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(methods of treating vascular diseases characterized by nitric oxide insufficiency)

IT **125978-95-2**, Nitric oxide synthase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(substrate; methods of treating vascular diseases characterized by nitric oxide insufficiency)

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L111 ANSWER 7 OF 18 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:666601 CAPLUS
DOCUMENT NUMBER: 133:256811
TITLE: Pharmaceutical compositions containing dopamine agonists in combination with nitric oxide donors for treating and/or preventing sexual dysfunctions
INVENTOR(S): Garvey, David S.
PATENT ASSIGNEE(S): Nitromed, Inc., USA
SOURCE: PCT Int. Appl., 48 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000054773	A1	20000921	WO 2000-US3709	20000310

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 1999-123920P P 19990312
OTHER SOURCE(S): MARPAT 133:256811
ED Entered STN: 22 Sep 2000
AB The present invention is directed to novel compns. comprising at least one dopamine agonist in combination with at least one nitric oxide donor (i.e. compds. that donate, transfer or release nitric oxide, elevate endogenous levels of endothelium-derived relaxing factor, stimulate endogenous synthesis of nitric oxide or are substrates for nitric oxide synthase). The novel compns. may optionally comprise at least one therapeutic agent, such as, a vasoactive agent, an antiemetic agent, and mixts. thereof. The dopamine agonist is preferably apomorphine. The present invention is also directed to methods for treating and/or preventing sexual dysfunctions and/or enhancing sexual responses in patients. In other embodiments, the present invention is directed to methods treating or preventing neurodegenerative diseases, mitochondrial diseases, spinal cord injury, central or psychostimulant addiction, senile dementia, circulatory disorders, cardiovascular disorders, hyperprolactinemia or myopia. The compds. and/or compns. of the present invention can also be provided in the form of a pharmaceutical kit (no data).
IT **372-75-8**, Citrulline **125978-95-2**, Nitric oxide synthase
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceutical compns. contg. dopamine **agonists** in combination with nitric oxide donors for treating and/or preventing sexual dysfunctions)
REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L111 ANSWER 8 OF 18 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1992:52189 CAPLUS
DOCUMENT NUMBER: 116:52189
TITLE: Glutamate receptor agonists stimulate nitric oxide

synthase in primary cultures of cerebellar granule cells
AUTHOR(S): Kiedrowski, Lech; Costa, Erminio; Wroblewski, Jarda T.
CORPORATE SOURCE: Sch. Med., Georgetown Univ., Washington, DC, 20007, USA
SOURCE: Journal of Neurochemistry (1992), 58(1), 335-41
CODEN: JONRA9; ISSN: 0022-3042
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 21 Feb 1992
AB The glutamate receptor agonist NMDA stimulated a rapid, extracellular Ca2+-dependent conversion of [3H]arginine to [3H]citrulline in primary cultures of cerebellar granule cells, indicating receptor-mediated activation of NO synthase. The NMDA-induced formation of [3H]citrulline reached a plateau within 10 min. Subsequent addn. of unlabeled L-arginine resulted in the disappearance of 3H from the citrulline pool, indicating a persistent activation of NO synthase after NMDA receptor stimulation. Glutamate, NMDA, and kainate, but not quisqualate, stimulated both the conversion of [3H]arginine to [3H]citrulline and cGMP accumulation in a dose-dependent manner. Glutamate and NMDA showed similar potencies for the stimulation of [3H]cirtulline formation and cGMP synthesis, resp., whereas kainate was more potent at inducing cGMP accumulation than at stimulating [3H]citrulline formation. Both the [3H]arginine to [3H]citrulline conversion and cGMP synthesis stimulated by NMDA were inhibited by the NMDA receptor antagonist MK 801 and by the inhibitors of NO synthase, NG-monomethyl-L-arginine (MeArg) and NG-nitro-L-arginine (NOArg). However, MeArg, in contrast to NOArg, also potently inhibited [3H]arginine uptake. Kainate (300 .mu.M) stimulated 45Ca2+ influx to the same extent as 100 .mu.M NMDA, but stimulated [3H]citrulline formation to a much lesser extent, which suggests that NO synthase is localized in subcellular compartments where the Ca2+ concn. is regulated mainly by the NMDA receptor.
IT **372-75-8**, Citrulline
RL: FORM (Formation, nonpreparative)
(formation of, from arginine by cerebellum granule cell, glutamate receptor agonists stimulation of)
IT **125978-95-2**, Nitric oxide synthase
RL: PROC (Process)
(of cerebellum granule cells, glutamate receptor **agonists** stimulation of)

L111 ANSWER 9 OF 18 WPIDS COPYRIGHT 2004 THE THOMSON CORP on STN DUPLICATE 1
ACCESSION NUMBER: 2002-129909 [17] WPIDS
DOC. NO. CPI: C2002-039807
TITLE: Treatment of nitric oxide **deficiency** diseases e.g. atherosclerosis, restenosis, hypertension and Alzheimer's disease, involves **administering citrulline** or its analog in combination with other enhancing and modulating agent.
DERWENT CLASS: B05
INVENTOR(S): CHWALISZ, K; GARFIELD, R E; SHI, S
PATENT ASSIGNEE(S): (CHWA-I) CHWALISZ K; (GARF-I) GARFIELD R E; (SHIS-I) SHI S
COUNTRY COUNT: 1
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
US 2001056068	A1	20011227	(200217)*		17	A61K038-00

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
US 2001056068	A1	US 1998-34351	19980304

PRIORITY APPLN. INFO: US 1998-34351 19980304
INT. PATENT CLASSIF.:
MAIN: A61K038-00
SECONDARY: A61K031-47
BASIC ABSTRACT:
US2001056068 A UPAB: 20020313
NOVELTY - Treatment or prevention of nitric oxide **deficiency** syndrome or a disease in a mammal involves administering a first agent (I) and optionally a second agent (II) where both (I) and (II) are not a natural food source. (I) enhances the level of endogenous nitric oxide in the target tissue and (II) modulates or enhances **nitric oxide synthesis**.

DETAILED DESCRIPTION - Treatment or prevention of nitric oxide **deficiency** syndrome or a disease in a mammal involves administering a first agent (I) and optionally a second agent (II) where both (I) and (II) are not a natural food source. (I) enhances the level of endogenous nitric oxide in the target tissue and (II) modulates or enhances **nitric oxide synthesis**.

An INDEPENDENT CLAIM is also included for a pharmaceutical composition comprising a mixture of citrulline (A), **nitric oxide synthesis** substrate and/or nitric oxide donor (B) and optionally at least one of estrogen, progestin and a cardiovascular agent. The estrogen bioequivalent is estradiol (1 - 2) mg and progestin bioequivalent is injected progesterone (50 - 300) mg. (B) is present in an amount to raise the blood level of circulating L-arginine to at least 10 - 50 nmolar above the normally 50 - 100 nmolar circulating levels or raise the nitric oxide donor levels to 1 - 1000 nmolar.

ACTIVITY - Antiarteriosclerotic; Vasotropic; Hypotensive; Gynecological; Antidiabetic; Antiasthmatic; Antiinflammatory; Antiallergic; Immunosuppressive; Nootropic; Neuroprotective; Cerebroprotective; Tocolytic; Antinfertility.

The treatment of patients for specific disorders is described but no results are included.

MECHANISM OF ACTION - Endogenous nitric oxide level enhancer; **Nitric oxide synthesis** modulator.

USE - For treatment or prevention of nitric oxide **deficiency** syndrome or disease such as atherosclerosis, restenosis, hypertension, preeclampsia, intrauterine fetal growth retardation, altered motility of the intestinal tract, pyloric stenosis, diabetes mellitus, asthma, neonatal respiratory distress syndrome, pulmonary hypertension, adult respiratory distress syndrome, acute inflammation, resistance to infection, SLE-lupus, anaphylactic reaction, allograft rejection, Alzheimer's disease, stroke, growth hormone disorder or behavior changes. Also in treatment of a female mammal who has exhibited or is susceptible to develop preterm labor, early pregnancy loss, infertility, cervical dystocia, symptoms of climacterium or is a candidate for hormone replacement therapy (claimed).

ADVANTAGE - The compositions have no side effects.

Dwg.0/3
FILE SEGMENT: CPI
FIELD AVAILABILITY: AB; DCN
MANUAL CODES: CPI: B01-A01; B01-A02; B01-C04; B01-C05; B05-A01B; B05-C03; B06-A02; B07-A02A; B07-D04D; B07-D06; B07-E04; B10-A05; B10-A13D; B10-A17; B10-B03B;

B14-A01; B14-C03; B14-D01; B14-D01B; B14-D01C; B14-E10; B14-E10B; B14-F01; B14-F02; B14-F02B; B14-F07; B14-G02B; B14-G02C; B14-K01; B14-K01A; B14-K01F; B14-L01; B14-N01; B14-N07D; B14-N14; B14-N16; B14-N17; B14-P02; B14-P03; B14-R02; B14-S04

L111 ANSWER 10 OF 18 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 2003445694 EMBASE

TITLE: Recombinant arginine deiminase as a differential modulator of inducible (iNOS) and endothelial (eNOS) nitric oxide synthetase activity in cultured endothelial cells.

AUTHOR: Shen L.-J.; Lin W.-C.; Beloussow K.; Hosoya K.-I.; Terasaki T.; Ann D.K.; Shen W.-C.

CORPORATE SOURCE: W.-C. Shen, Dept. of Pharmaceutical Sciences, School of Pharmacy, University of Southern California, 1985 Zonal Avenue 404B, Los Angeles, CA 90089-9121, United States. weishen@usc.edu

SOURCE: Biochemical Pharmacology, (15 Nov 2003) 66/10 (1945-1952). Refs: 30
ISSN: 0006-2952 CODEN: BCPCA6

COUNTRY: United States

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 030 Pharmacology
037 Drug Literature Index

LANGUAGE: English

SUMMARY LANGUAGE: English

ABSTRACT:

Modulation of the extracellular level of arginine, substrate for nitric oxide synthetases, is a promising modality to alleviate certain pathological conditions where excess nitric oxide (NO) is produced. However, complications arise, as only preferential inhibition of the inducible nitric oxide synthetase (iNOS), but not endothelial nitric oxide synthetase (eNOS), is desired for the treatment of NO over-production. We investigated the effect of arginine deprivation mediated by a recombinant arginine deiminase (rADI) on the activity of iNOS and eNOS in an endothelial cell line, TR-BBB. Our results demonstrated that cytokine-induced NO production depends on the extracellular arginine as substrate. However, if sufficient citrulline is present in the medium, A23187-activated NO production by eNOS does not rely on extracellular arginine. Treatment with rADI can markedly inhibit cytokine-induced NO production via iNOS, but not A23187-activated NO production via eNOS. Our results also showed that the decrease of NO production by iNOS could be achieved by depleting arginine from the medium even under the conditions that would up-regulate iNOS expression. Thus, rADI appears to be a novel selective modulator of iNOS activity that may be a used as a tool in the study of pathological disorders where NO over-production plays a key role.

CONTROLLED TERM: Medical Descriptors:
enzyme activity
endothelium cell
cell culture
drug effect
enzyme substrate
culture medium
upregulation
protein expression
drug selectivity
enzyme regulation
drug mechanism
depletion
nonhuman

rat
controlled study
animal cell
article
priority journal
Drug Descriptors:
*recombinant enzyme: PD, pharmacology
*recombinant arginine deiminase: PD, pharmacology
***nitric oxide synthase**
*inducible nitric oxide synthase
*endothelial nitric oxide synthase
*arginine deiminase
cytokine
arginine
citrulline: PD, pharmacology
calcimycin: PD, pharmacology
nitric oxide
unclassified drug
CAS REGISTRY NO.: (nitric oxide synthase) 125978-95-2; (arginine deiminase) 9027-98-9, 9074-85-5; (arginine) 1119-34-2, 15595-35-4, 7004-12-8, 74-79-3; (citrulline) 372-75-8; (calcimycin) 52665-69-7; (nitric oxide) 10102-43-9
CHEMICAL NAME: (1) A 23187
COMPANY NAME: (1) Sigma

L111 ANSWER 11 OF 18 EMBASE
on STN
ACCESSION NUMBER: 2002426652 EMBASE
TITLE: Hemodynamics of early tubuloglomerular feedback resetting during reduced proximal reabsorption.
AUTHOR: Deng A.; Hammes J.S.; Thomson S.C.
CORPORATE SOURCE: Dr. S.C. Thomson, Division of Nephrology/Hypertension, Department of Medicine, University of California and VAMC, 3350 La Jolla Village Drive, San Diego, CA 92161-9151, United States. sthomson@ucsd.edu
SOURCE: Kidney International, (2002) 62/6 (2136-2143).
Refs: 23
ISSN: 0085-2538 CODEN: KDYIA5
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 028 Urology and Nephrology
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ABSTRACT:
Background. Carbonic anhydrase inhibition with benzolamide reduces proximal reabsorption and activates tubuloglomerular feedback (TGF). In rats, TGF activation for 30 to 60 minutes locally suppresses renin secretion and resets TGF rightward to accommodate increased late proximal flow. After 24 hours of TGF activation, there is upward resetting of GFR and increased activity of macula densa nitric oxide synthase I (NOS I). Methods. We studied renal hemodynamics during early TGF resetting with attention to the importance of renin suppression and NOS I activation. Left kidney blood flow (RBF, pulse Doppler) and glomerular filtration rate (GFR; inulin clearance or Fick method) were measured before and during benzolamide infusion (5 mg/kg bolus followed by 5 mg/kg/h IV) in Wistar rats concurrently receiving the converting enzyme inhibitor, enalaprilat (0.3 mg/kg/h IV) or NOS-I blocker S-methyl-thiocitrulline (SMTC; 2.7 mg/kg/h IV). Results. Activating TGF initially reduced RBF and GFR in all groups as expected. During continuous benzolamide, RBF gradually increased toward baseline in control and enalaprilat-treated rats, but not in NOS I-blocked rats. After the initial decline, GFR did not

change further during one hour of benzolamide in any group. Conclusions. During one hour of persistent TGF stimulation, RBF increases toward normal, but GFR does not. This requires an overall decrease in renal vascular resistance and a decrease in the ratio of efferent/afferent arteriolar resistance (R(E)/R(A)), implying a major decrease in R(E). NOS I, but not angiotensin-converting enzyme (ACE), is required for RBF to increase during TGF resetting. Although the hemodynamic changes during TGF resetting resemble the response to blocking the renin-angiotensin system, these data fail to show that the increase in RBF during early TGF resetting is mediated by renin suppression.

CONTROLLED TERM: Medical Descriptors:
*glomerulus filtration rate
*kidney proximal tubule
*macula densa
hemodynamics
enzyme activation
kidney blood flow
inulin clearance
enzyme inhibition
nonhuman
male
rat
animal experiment
controlled study
animal tissue
article
priority journal
Drug Descriptors:
***nitric oxide synthase: EC, endogenous compound**
enalaprilat: PD, pharmacology
enalaprilat: IV, intravenous drug administration
citrulline: PD, pharmacology
citrulline: IV, intravenous drug administration
benzolamide
dipeptidyl carboxypeptidase: EC, endogenous compound
renin: EC, endogenous compound
inulin: EC, endogenous compound

CAS REGISTRY NO.: (nitric oxide synthase) 125978-95-2; (enalaprilat) 76420-72-9; (citrulline) 372-75-8; (benzolamide) 3368-13-6; (dipeptidyl carboxypeptidase) 9015-82-1; (renin) 61506-93-2, 9015-94-5; (inulin) 9005-80-5

COMPANY NAME: Sigma (United States)

L111 ANSWER 12 OF 18 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 2002155492 EMBASE

TITLE: Progress in the development of selective nitric oxide synthase (NOS) inhibitors.

AUTHOR: Salerno L.; Sorrenti V.; Di Giacomo C.; Romeo G.; Siracusa M.A.

CORPORATE SOURCE: L. Salerno, Dipartimento Scienze Farmaceutiche, Universita di Catania, Chimica Medica e Biologia Molecolare, Viale A. Doria 6, 95125 Catania, Italy. L.Salerno@mbox.unict.it

SOURCE: Current Pharmaceutical Design, (2002) 8/3 (177-200).
Refs: 147
ISSN: 1381-6128 CODEN: CPDEFP

COUNTRY: Netherlands

DOCUMENT TYPE: Journal; General Review

FILE SEGMENT: 008 Neurology and Neurosurgery
029 Clinical Biochemistry
030 Pharmacology
037 Drug Literature Index

LANGUAGE: English
SUMMARY LANGUAGE: English
ABSTRACT:
Nitric oxide (NO), a molecular messenger synthesized by nitric oxide synthase (NOS) from L-arginine and molecular oxygen, is involved in a number of physiological and pathological processes in mammalians. Three structurally distinct isoforms of NOS have been identified: neuronal (nNOS), endothelial (eNOS) and inducible (iNOS). Although NO mediates several physiological functions, overproduction of NO by nNOS has been reported in a number of clinical disorders including acute (stroke) and chronic (schizophrenia, Alzheimer's, Parkinson's and AIDS dementia) neurodegenerative diseases, convulsions and pain; overproduction of NO by iNOS has been implicated in various pathological processes including septic shock, tissue damage following inflammation and rheumatoid arthritis. On the contrary, NO produced by eNOS has only physiological roles such as maintaining physiological vascular tone. Accordingly, selective inhibition of nNOS or iNOS vs eNOS may provide a novel therapeutic approach to various diseases; in addition selective inhibitors may represent useful tools for investigating other biological functions of NO. For these reasons, after the identification of N-methyl-L-arginine (L-NMA) as the first inhibitor of NO biosynthesis, design of selective NOS inhibitors has received much attention.

CONTROLLED TERM: Medical Descriptors:
drug selectivity
enzyme synthesis
mammal
enzyme structure
nerve cell
endothelium
enzyme induction
physiology
stroke
schizophrenia
Alzheimer disease
Parkinson disease
acquired immune deficiency syndrome
dementia
degenerative disease
convulsion
pain
septic shock
tissue injury
inflammation
rheumatoid arthritis
blood vessel tone
enzyme inhibition
biosynthesis
drug design
structure activity relation
human
nonhuman
mouse
rat
animal experiment
animal model
controlled study
review
priority journal
Drug Descriptors:
*nitric oxide synthase inhibitor: AN, drug analysis
*nitric oxide synthase inhibitor: DV, drug development
*nitric oxide synthase inhibitor: PD, pharmacology

nitric oxide: EC, endogenous compound
nitric oxide synthase: EC, endogenous compound
arginine: EC, endogenous compound
oxygen: EC, endogenous compound
isoenzyme: EC, endogenous compound
arginine derivative: AN, drug analysis
arginine derivative: DV, drug development
arginine derivative: PD, pharmacology
citrulline: AN, drug analysis
citrulline: DV, drug development
citrulline: PD, pharmacology
guanidine derivative: AN, drug analysis
guanidine derivative: DV, drug development
guanidine derivative: PD, pharmacology
thiourea derivative: AN, drug analysis
thiourea derivative: DV, drug development
thiourea derivative: PD, pharmacology
n (2 methyl 1,2,3,4 tetrahydroisoquinolin 7 yl) 2
thiophenecarboxamidine: AN, drug analysis
n (2 methyl 1,2,3,4 tetrahydroisoquinolin 7 yl) 2
thiophenecarboxamidine: CM, drug comparison
n (2 methyl 1,2,3,4 tetrahydroisoquinolin 7 yl) 2
thiophenecarboxamidine: PD, pharmacology
amidine: AN, drug analysis
amidine: DV, drug development
amidine: PD, pharmacology
indazole derivative: AN, drug analysis
indazole derivative: DV, drug development
indazole derivative: PD, pharmacology
imidazole: AN, drug analysis
imidazole: DV, drug development
imidazole: PD, pharmacology
tetrahydrobiopterin: AN, drug analysis
tetrahydrobiopterin: DV, drug development
tetrahydrobiopterin: PD, pharmacology
2 benzoxazolone derivative: AN, drug analysis
2 benzoxazolone derivative: DV, drug development
2 benzoxazolone derivative: PD, pharmacology
ornithine derivative: AN, drug analysis
ornithine derivative: CM, drug comparison
ornithine derivative: PD, pharmacology
homocitrulline: AN, drug analysis
homocitrulline: CM, drug comparison
homocitrulline: PD, pharmacology
aminoguanidine: AN, drug analysis
aminoguanidine: CM, drug comparison
aminoguanidine: PD, pharmacology
aminoethylisothiouronium: AN, drug analysis
aminoethylisothiouronium: CM, drug comparison
aminoethylisothiouronium: PD, pharmacology
ethyl n [4 (trifluoromethyl)phenyl] isothiourea: AN, drug analysis
ethyl n [4 (trifluoromethyl)phenyl] isothiourea: CM, drug comparison
ethyl n [4 (trifluoromethyl)phenyl] isothiourea: PD, pharmacology
antioxidant: AN, drug analysis
antioxidant: CM, drug comparison
antioxidant: PD, pharmacology
4 phenylimidazole: AN, drug analysis
4 phenylimidazole: CM, drug comparison
4 phenylimidazole: PD, pharmacology

pyridine derivative: AN, drug analysis
pyridine derivative: DV, drug development
pyridine derivative: PD, pharmacology
2 amino 4 picoline: AN, drug analysis
2 amino 4 picoline: CM, drug comparison
2 amino 4 picoline: PD, pharmacology
n [4 [4 [(3,4 dihydro 6 hydroxy 2,5,7,8 tetramethyl 2h 1 benzopyran 2 yl)carbonyl] 1 piperazinyl]phenyl] 2 thiophenecarboximidamide: AN, drug analysis
n [4 [4 [(3,4 dihydro 6 hydroxy 2,5,7,8 tetramethyl 2h 1 benzopyran 2 yl)carbonyl] 1 piperazinyl]phenyl] 2 thiophenecarboximidamide: CM, drug comparison
n [4 [4 [(3,4 dihydro 6 hydroxy 2,5,7,8 tetramethyl 2h 1 benzopyran 2 yl)carbonyl] 1 piperazinyl]phenyl] 2 thiophenecarboximidamide: PD, pharmacology
pyrazole derivative: AN, drug analysis
pyrazole derivative: CM, drug comparison
pyrazole derivative: PD, pharmacology
heme
phenylthiourea: AN, drug analysis
phenylthiourea: CR, drug concentration
phenylthiourea: PD, pharmacology
unindexed drug
unclassified drug
ar r 18512

CAS REGISTRY NO.: (nitric oxide) 10102-43-9; (nitric oxide synthase) 125978-95-2; (arginine) 1119-34-2, 15595-35-4, 7004-12-8, 74-79-3; (oxygen) 7782-44-7; (citrulline) 372-75-8; (imidazole) 1467-16-9, 288-32-4; (tetrahydrobiopterin) 17528-72-2; (homocitrulline) 1190-49-4; (aminoguanidine) 1068-42-4, 2582-30-1, 79-17-4; (aminoethylisothiouronium) 151-16-6, 55818-78-5, 56-10-0; (4 phenylimidazole) 670-95-1; (2 amino 4 picoline) 695-34-1; (n [4 [4 [(3,4 dihydro 6 hydroxy 2,5,7,8 tetramethyl 2h 1 benzopyran 2 yl)carbonyl] 1 piperazinyl]phenyl] 2 thiophenecarboximidamide) 214348-10-4; (heme) 14875-96-8; (phenylthiourea) 103-85-5

CHEMICAL NAME: Ar r 18512; Bn 80933

L111 ANSWER 13 OF 18 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 2002047132 EMBASE
TITLE: The arginine paradox.
AUTHOR: Nakaki T.; Hishikawa K.
CORPORATE SOURCE: T. Nakaki, Department of Pharmacology, Teikyo University School of Medicine, 2-11-1 Kaga, Itabashi-ku, Tokyo 173-8605, Japan. nakaki@med.teikyo-u.ac.jp
SOURCE: Folia Pharmacologica Japonica, (2002) 119/1 (7-14).
Refs: 58
ISSN: 0015-5691 CODEN: NYKZAU
COUNTRY: Japan
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 029 Clinical Biochemistry
037 Drug Literature Index
LANGUAGE: Japanese
SUMMARY LANGUAGE: English; Japanese
ABSTRACT:

L-Arginine has attracted major interest because it has been identified as the natural substrate of nitric oxide synthase and is now recognized as a major player in the regulation of biological function. The arginine paradox refers to the phenomenon that exogenous L-arginine causes NO-mediated biological effects despite the fact that nitric oxide synthases (NOS) are theoretically saturated

with the substrate L-arginine. There have been several explanations for this phenomenon, although none of them can explain the arginine paradox fully: (1) L-arginine-induced insulin, which has vasodilatory actions. (2) Neither extracellular nor intracellular concentration determines the NOS activity but rather the L-arginine amount transported across the plasma membrane may do so. (3) Endogenous NOS inhibitors reduce the enzyme sensitivity to L-arginine. These inhibitors include, N(G), N(G)-dimethyl-L-arginine, L-citrulline, argininosuccinic acid and agmatine. (4) Intracellular L-citrulline, an NOS product, is a potent inhibitor of NOS so that the cells may need extra L-arginine to compete with L-citrulline inhibition.

CONTROLLED TERM: Medical Descriptors:
vasodilatation
insulin release
enzyme activity
amino acid transport
membrane transport
drug activity
enzyme kinetics
human
review
Drug Descriptors:
*arginine: EC, endogenous compound
***nitric oxide synthase: EC, endogenous compound**
*nitric oxide: EC, endogenous compound
*nitric oxide synthase inhibitor: PD, pharmacology
insulin: EC, endogenous compound
n(g),n(g) dimethylarginine: PD, pharmacology
citrulline: PD, pharmacology
argininosuccinic acid: PD, pharmacology
agmatine: PD, pharmacology

CAS REGISTRY NO.: (arginine) 1119-34-2, 15595-35-4, 7004-12-8, 74-79-3; (nitric oxide synthase) 125978-95-2; (nitric oxide) 10102-43-9; (insulin) 9004-10-8; (n(g),n(g) dimethylarginine) 30315-93-6; (citrulline) 372-75-8; (argininosuccinic acid) 2387-71-5, 28643-94-9; (agmatine) 306-60-5

L111 ANSWER 14 OF 18 EMBASE
on STN

ACCESSION NUMBER: 96067882 EMBASE
DOCUMENT NUMBER: 1996067882
TITLE: Selective pharmacological inhibition of distinct nitric oxide synthase isoforms.
AUTHOR: Southan G.J.; Szabo C.
CORPORATE SOURCE: Division of Critical Care, Children's Hospital Medical Center, 3333 Burnet Ave.,Cincinnati, OH 45229, United States
SOURCE: Biochemical Pharmacology, (1996) 51/4 (383-394).
ISSN: 0006-2952 CODEN: BCPCA6
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 002 Physiology
005 General Pathology and Pathological Anatomy
029 Clinical Biochemistry
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
ABSTRACT:
Nitric oxide (NO) is produced in physiological and pathophysiological

conditions by three distinct isoforms of NO synthase (NOS): endothelial NOS (ecNOS), inducible NOS (iNOS), and brain NOS (bNOS). Selective inhibition of iNOS may be beneficial in various forms of shock and inflammation, whereas inhibition of bNOS may protect against neuroinjury. This article surveys the enzymatic mechanism of NO production, lists the strategies and pharmacological tools for selective inhibition of distinct NOS isoforms, and considers the side-effects of the various approaches. Selective inhibition of NOS isoforms is achieved by: (a) targeting the differential co-factor (calmodulin or tetrahydrobiopterin) requirement of various NOS isoforms of NOS; (b) targeting the differential substrate requirements of cells expressing various isoforms of NOS (L-arginine uptake blockers or arginase); (c) the use of pharmacological agents that are selectively taken up by cells expressing various isoforms of NOS (7-nitroindazole); or (d) developing pharmacological NOS inhibitors with isoform specificity. The amino acid-based NOS inhibitor, N(G)-nitro-L-arginine, shows a preference for ecNOS and bNOS over iNOS, whereas L-N6-(1-iminoethyl)lysine is selective for iNOS over bNOS. Certain non-amino acid-based small molecules, such as aminoguanidine and certain S-alkylated isothioureas, also express selectivity towards iNOS and have anti-inflammatory and anti-shock properties. 7-Nitroindazole, a bNOS-selective inhibitor, protects in central nervous system injury. Clearly, there are a number of distinct approaches that are worthy of further research efforts in order to achieve even more selective targeting of various NOS isoforms.

CONTROLLED TERM:

Medical Descriptors:
*brain injury
*inflammation
*macrophage
*shock
*vascular endothelium
animal model
drug selectivity
drug targeting
enzyme induction
human
nerve cell degeneration: SI, side effect
nonhuman
pathophysiology
physiology
priority journal
review
structure activity relation
Drug Descriptors:
*isoenzyme: EC, endogenous compound
*nitric oxide: EC, endogenous compound
***nitric oxide synthase: EC, endogenous compound**
*nitric oxide synthase inhibitor: AE, adverse drug reaction
*nitric oxide synthase inhibitor: PD, pharmacology
7 nitroindazole: PD, pharmacology
amidine: PD, pharmacology
aminoguanidine: PD, pharmacology
arginine derivative: PD, pharmacology
calmodulin: EC, endogenous compound
citrulline: PD, pharmacology
ebselen: PD, pharmacology
ebselen derivative: PD, pharmacology
guanidine derivative: PD, pharmacology
homoarginine: PD, pharmacology
imidazole derivative: PD, pharmacology
methylene blue: PD, pharmacology
n(g) allylarginine: PD, pharmacology
n(g) aminoarginine: PD, pharmacology
n(g) cyclopropylarginine: PD, pharmacology

n(g) hydroxyarginine: PD, pharmacology
n(g) methylarginine: PD, pharmacology
n(g) nitroarginine: PD, pharmacology
n(g) nitroarginine methyl ester: PD, pharmacology
n5 (1 iminoethyl)ornithine: PD, pharmacology
n6 (1 iminoethyl)lysine: PD, pharmacology
pseudothiourea derivative: PD, pharmacology
s ethylthiocitrulline: PD, pharmacology
s methylthiocitrulline: PD, pharmacology
tetrahydrobiopterin: EC, endogenous compound
thiocitrulline: PD, pharmacology
unindexed drug
unclassified drug

CAS REGISTRY NO.: (nitric oxide) 10102-43-9; (nitric oxide synthase) 125978-95-2; (7 nitroindazole) 2942-42-9; (aminoguanidine) 1068-42-4, 2582-30-1, 79-17-4; (citrulline) 372-75-8; (ebselen) 60940-34-3; (homoarginine) 156-86-5; (methylene blue) 61-73-4; (n(g) methylarginine) 17035-90-4; (n(g) nitroarginine) 2149-70-4; (n(g) nitroarginine methyl ester) 50903-99-6; (n5 (1 iminoethyl)ornithine) 36889-13-1; (tetrahydrobiopterin) 17528-72-2

L111 ANSWER 15 OF 18 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 95232088 EMBASE
DOCUMENT NUMBER: 1995232088
TITLE: Expression of the citrulline-nitric oxide cycle in rodent and human pancreatic .beta.-cells: Induction of argininosuccinate synthetase by cytokines.
AUTHOR: Flodstrom M.; Niemann A.; Bedoya F.J.; Morris Jr. S.M.; Eizirik D.L.
CORPORATE SOURCE: Department of Medical Cell Biology, Uppsala University, P.O. Box 571,S-751 23 Uppsala, Sweden
SOURCE: Endocrinology, (1995) 136/8 (3200-3206).
ISSN: 0013-7227 CODEN: ENDOAO
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 003 Endocrinology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ABSTRACT:
Nitric oxide (NO) may be a mediator of .beta.-cell damage in insulin- dependent diabetes mellitus. .beta.-Cells express the inducible form of NO synthase (iNOS) and produce large amounts of NO upon exposure to cytokines. iNOS requires the amino acid arginine for NO formation. It has been shown in other cell types that interferon-.gamma. (IFN.gamma.) and bacterial lipopolysaccharide induce the enzyme argininosuccinate synthetase (AS), enhancing the capacity of these cells to regenerate arginine from citrulline and maintain NO production in the presence of low arginine concentrations. To characterize the messenger RNA (mRNA) expression of AS in insulin-producing cells, RINm5F cells (RIN cells) were exposed to interleukin-1.beta. (IL-1.beta.) or to tumor necrosis factor-.alpha. plus IFN.gamma.. After 4-6 h, there was a significant and parallel induction of AS and iNOS mRNA. IL-1.beta.-induced AS and iNOS mRNA expression was prevented by an inhibitor of the activation factor NF-.kappa.B pyrrolidine diaminoguanidine, an inhibitor of gene transcription (actinomycin D), and a blocker of protein synthesis (cycloheximide), suggesting coregulation of AS and iNOS by cytokines. RIN cells exposed to IL-1.beta. in the presence of citrulline but the absence of arginine had increased AS enzyme activity and produced NO, demonstrating that cytokine-induced AS mRNA expression is accompanied by increased AS activity. Both adult rat islets exposed to IL-1.beta. and human pancreatic islets

cultured in the presence of IL- 1.beta., tumor necrosis factor-.alpha., and IFN.gamma. were able to use citrulline to regenerate arginine and produce NO. Taken as a whole, the present data suggest that regulation of AS activity may play a role in modulation of NO production in both rodent and human insulin-producing cells.

CONTROLLED TERM: Medical Descriptors:
*oxidation
*pancreas islet beta cell
animal cell
animal tissue
article
cell damage
cell regeneration
controlled study
enzyme induction
enzyme regulation
gene expression regulation
human
human cell
human tissue
immunomodulation
insulin dependent diabetes mellitus: ET, etiology
nonhuman
priority journal
rat
Drug Descriptors:
*argininosuccinate synthase: EC, endogenous compound
*gamma interferon: PD, pharmacology
*nitric oxide: EC, endogenous compound
***nitric oxide synthase: PD, pharmacology**
citrulline: PD, pharmacology
cycloheximide: PD, pharmacology
dactinomycin: PD, pharmacology
interleukin 1beta: PD, pharmacology
messenger rna: EC, endogenous compound
tumor necrosis factor: PD, pharmacology

CAS REGISTRY NO.: (argininosuccinate synthase) 9023-58-9; (gamma interferon) 82115-62-6; (nitric oxide) 10102-43-9; (nitric oxide synthase) 125978-95-2; (citrulline) 372-75-8; (cycloheximide) 642-81-9, 66-81-9; (dactinomycin) 1402-38-6, 1402-58-0, 50-76-0

L111 ANSWER 16 OF 18 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 95324331 EMBASE
DOCUMENT NUMBER: 1995324331
TITLE: Nitric oxide: Physiology and pharmacology.
AUTHOR: Schroeder R.A.; Kuo P.C.
CORPORATE SOURCE: Department of Anesthesia, University of California, Box 0648, 521 Parnassus Avenue,San Francisco, CA 94143-0648, United States
SOURCE: Anesthesia and Analgesia, (1995) 81/5 (1052-1059). ISSN: 0003-2999 CODEN: AACRAT
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 024 Anesthesiology
037 Drug Literature Index
LANGUAGE: English

CONTROLLED TERM: Medical Descriptors:
*analgesia

*anesthesia
cardiovascular function
clinical practice
enzyme activity
homeostasis
immunoregulation
intensive care
priority journal
review
signal transduction
Drug Descriptors:
*nitric oxide: PD, pharmacology
***nitric oxide synthase: EC, endogenous compound**
citrulline: PD, pharmacology
CAS REGISTRY NO.: (nitric oxide) 10102-43-9; (nitric oxide synthase) 125978-95-2; (citrulline) 372-75-8

L111 ANSWER 17 OF 18 USPATFULL on STN
ACCESSION NUMBER: 2000:21601 USPATFULL
TITLE: Orthomolecular medical use of L-citrulline for vasoprotection, relaxative smooth muscle tone and cell protection
INVENTOR(S): Waugh, William Howard, 119 Oxford Rd., Greenville, NC, United States 27858

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6028107		20000222
APPLICATION INFO.:	US 1997-807757		19970227 (8)

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Dees, Jose' G.
ASSISTANT EXAMINER: Qazi, Sabiha N.
NUMBER OF CLAIMS: 19
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 1 Drawing Figure(s); 1 Drawing Page(s)
LINE COUNT: 1141
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB This invention is a novel method in orthomolecular medicine to sustain favorable amounts of L-arginine efficiently within the human body for preservation of good health and amelioration of various disease states. The method provides **administration** of sizable amounts of L-**citrulline** as precursor substance for bioconversion to L-arginine in order to maintain greater blood plasma concentrations of L-arginine as potential substrate for various metabolic functions. The method is useful to increase the availability of substrate for nitric oxide production by constitutive nitric oxide synthases. Embodiments include uses of exogenous L-citrulline for more vasoprotection in sickle cell disease and atherosclerosis, more stability in circulating platelets, more relaxative smooth muscle tone during pregnancy and in achalasia, greater defense against restenosis after angioplasty, greater defense against oxidative stress, enhanced cell stores of creatine, and enhanced fertility in males with oligospermia.
IT **372-75-8**, L-Citrulline
(citrulline in orthomol. medicine for vasoprotection, relaxive toning of smooth muscles, and other therapeutic uses)

L111 ANSWER 18 OF 18 USPATFULL on STN
ACCESSION NUMBER: 1999:24689 USPATFULL

TITLE: Orthomolecular medical use of L-citrulline for vasoprotection, relaxative smooth muscle tone and cell protection

INVENTOR(S): Waugh, William Howard, 119 Oxford Rd., Greenville, NC, United States 27858

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5874471		19990223
APPLICATION INFO.:	US 1997-961639		19971030 (8)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 1997-807757, filed on 27 Feb 1997
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Henley, III, Raymond
NUMBER OF CLAIMS: 30
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 1 Drawing Figure(s); 1 Drawing Page(s)
LINE COUNT: 1339
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB This invention is a novel method in orthomolecular health to sustain favorable amounts of L-arginine efficiently within the human body for preservation of good health and amelioration of various disease states. The method provides **administration** of sizable amounts of L-**citrulline** as precursor substance for bioconversion to L-arginine in order to maintain greater blood plasma concentrations of L-arginine as potential substrate for various metabolic functions. The method is useful to increase the availability of substrate for nitric oxide production by constitutive nitric oxide synthases. Embodiments include uses of exogenous L-citrulline for more vasoprotection in sickle cell disease and atherosclerosis, more stability in circulating platelets, more relaxative smooth muscle tone during pregnancy and in achalasia, greater defense against angiostenosis after angioplasty, greater defense against oxidative stress, enhanced cell stores of creatine, enhanced fertility in males with oligospermia, and greater defense against osteoporosis.

IT **372-75-8**, L-Citrulline
(orthomol. medical use of L-citrulline for vasoprotection, relaxative smooth muscle tone, and cell protection)

FILE 'HOME' ENTERED AT 12:55:30 ON 23 SEP 2004

```
=> fil reg; d ide l112
FILE 'REGISTRY' ENTERED AT 13:10:48 ON 23 SEP 2004
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STRUCTURE FILE UPDATES:   22 SEP 2004  HIGHEST RN 749824-02-0
DICTIONARY FILE UPDATES:  22 SEP 2004  HIGHEST RN 749824-02-0

TSCA INFORMATION NOW CURRENT THROUGH MAY 21, 2004

  Please note that search-term pricing does apply when
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Crossover limits have been increased.  See HELP CROSSOVER for details.

Experimental and calculated property data are now available. For more
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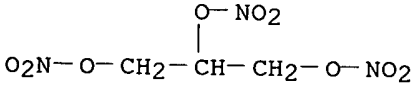
http://www.cas.org/ONLINE/DBSS/registryss.html


L112 ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2004 ACS on STN
RN   55-63-0  REGISTRY
CN   1,2,3-Propanetriol, trinitrate (9CI)  (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN   Nitroglycerin (8CI)
OTHER NAMES:
CN   1,2,3-Propanetriyl nitrate
CN   Adesitrin
CN   Angibid
CN   Anginine
CN   Angiolingual
CN   Angorin
CN   Aquo-Trinitrosan
CN   Blasting oil
CN   Cardamist
CN   Chitamite
CN   Cordipatch
CN   Corditrine
CN   Coro-Nitro
CN   Deponit
CN   Diafusor
CN   Discotrine
CN   Epinitril
CN   Gilucor
CN   Gilucor nitro
CN   Glonoin
CN   Glycerin trinitrate
CN   Glycerol nitric acid triester
CN   Glycerol trinitrate
CN   Glyceryl nitrate
CN   Glyceryl trinitrate
CN   GTN
CN   Klavikordal
CN   Lenitral
CN   Lentonitrina
```

CN Millisrol
CN Minitran
CN Minitran (nitroglycerin)
CN Myoglycerin
CN NG
CN Niglin
CN Niglycon
CN Niong
CN Nitora
CN Nitrin
CN Nitrine
CN Nitrine-TDC
CN Nitro Mack
CN Nitro-Bid
CN Nitro-Dur
CN Nitro-Gesani
CN Nitro-lent
CN Nitro-PRN
CN Nitro-Span
CN Nitrocardin
CN Nitroderm
ADDITIONAL NAMES NOT AVAILABLE IN THIS FORMAT - Use FCN, FIDE, or ALL for DISPLAY
FS 3D CONCORD
DR 8013-23-8, 9010-02-0, 105469-31-6, 80066-48-4, 100292-13-5
MF C3 H5 N3 O9
CI COM
LC STN Files: ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, AQUIRE, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CBNB, CEN, CHEMCATS, CHEMINFORMRX, CHEMLIST, CHEMSAFE, CIN, CSCHEM, CSNB, DDFU, DETHERM*, DIOGENES, DIPPR*, DRUGU, EMBASE, GMELIN*, HODOC*, HSDB*, IFICDB, IFIPAT, IFIUDB, IMSCOSEARCH, IMSDRUGNEWS, IMSPATENTS, IMSRESEARCH, IPA, MEDLINE, MRCK*, MSDS-OHS, NIOSHTIC, PDLCOM*, PHAR, PIRA, PROMT, RTECS*, SPECINFO, TOXCENTER, TULSA, ULIDAT, USAN, USPAT2, USPATFULL, VETU, VTB
(*File contains numerically searchable property data)
Other Sources: DSL**, EINECS**, TSCA**
(**Enter CHEMLIST File for up-to-date regulatory information)
DT.CA CAplus document type: Book; Conference; Dissertation; Journal; Patent; Report
RL.P Roles from patents: ANST (Analytical study); BIOL (Biological study); MSC (Miscellaneous); OCCU (Occurrence); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses); NORL (No role in record)
RLD.P Roles for non-specific derivatives from patents: BIOL (Biological study); FORM (Formation, nonpreparative); PREP (Preparation); PROC (Process); USES (Uses)
RL.NP Roles from non-patents: ANST (Analytical study); BIOL (Biological study); FORM (Formation, nonpreparative); MSC (Miscellaneous); OCCU (Occurrence); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses); NORL (No role in record)
RLD.NP Roles for non-specific derivatives from non-patents: ANST (Analytical study); BIOL (Biological study); PROC (Process); PRP (Properties); USES (Uses)



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

7261 REFERENCES IN FILE CA (1907 TO DATE)
37 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
7266 REFERENCES IN FILE CAPLUS (1907 TO DATE)
7 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

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=> fil capl; d que l114
FILE 'CAPLUS' ENTERED AT 13:24:02 ON 23 SEP 2004
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FILE COVERS 1907 - 23 Sep 2004  VOL 141 ISS 13
FILE LAST UPDATED: 22 Sep 2004  (20040922/ED)

  This file contains CAS Registry Numbers for easy and accurate
  substance identification.

'OBI' IS DEFAULT SEARCH FIELD FOR 'CAPLUS' FILE


L3             1 SEA FILE=REGISTRY ABB=ON  CITRULLINE/CN
L4             1 SEA FILE=REGISTRY ABB=ON  L-CITRULLINE/CN
L5             1 SEA FILE=REGISTRY ABB=ON  "L-CITRULLINE HYDROCHLORIDE"/CN
L6             2 SEA FILE=REGISTRY ABB=ON  (L3 OR L4 OR L5)
L20         3622 SEA FILE=CAPLUS ABB=ON  L6
L112           1 SEA FILE=REGISTRY ABB=ON  NITROGLYCERIN/CN
L113        7272 SEA FILE=CAPLUS ABB=ON  L112
L114           3 SEA FILE=CAPLUS ABB=ON  L20 AND L113


=> s l114 not l110

L130           2 L114 NOT L110

=> fil uspatf; d que l117

FILE 'USPATFULL' ENTERED AT 13:24:03 ON 23 SEP 2004
CA INDEXING COPYRIGHT (C) 2004 AMERICAN CHEMICAL SOCIETY (ACS)

FILE COVERS 1971 TO PATENT PUBLICATION DATE: 23 Sep 2004 (20040923/PD)
FILE LAST UPDATED: 23 Sep 2004 (20040923/ED)
HIGHEST GRANTED PATENT NUMBER: US6795973
HIGHEST APPLICATION PUBLICATION NUMBER: US2004187181
CA INDEXING IS CURRENT THROUGH 23 Sep 2004 (20040923/UPCA)
ISSUE CLASS FIELDS (/INCL) CURRENT THROUGH: 23 Sep 2004 (20040923/PD)
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Jun 2004
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Jun 2004

>>>  USPAT2 is now available.  USPATFULL contains full text of the     <<<
>>>  original, i.e., the earliest published granted patents or         <<<
>>>  applications.  USPAT2 contains full text of the latest US         <<<
>>>  publications, starting in 2001, for the inventions covered in     <<<
>>>  USPATFULL.  A USPATFULL record contains not only the original     <<<
>>>  published document but also a list of any subsequent              <<<
```

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>>>  publications.  The publication number, patent kind code, and      <<<
>>>  publication date for all the US publications for an invention     <<<
>>>  are displayed in the PI (Patent Information) field of USPATFULL   <<<
>>>  records and may be searched in standard search fields, e.g., /PN, <<<
>>>  /PK, etc.                                                         <<<

>>>  USPATFULL and USPAT2 can be accessed and searched together        <<<
>>>  through the new cluster USPATALL.  Type FILE USPATALL to          <<<
>>>  enter this cluster.                                               <<<
>>>                                                                    <<<
>>>  Use USPATALL when searching terms such as patent assignees,       <<<
>>>  classifications, or claims, that may potentially change from      <<<
>>>  the earliest to the latest publication.                           <<<

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substance identification.


L3             1 SEA FILE=REGISTRY ABB=ON  CITRULLINE/CN
L4             1 SEA FILE=REGISTRY ABB=ON  L-CITRULLINE/CN
L5             1 SEA FILE=REGISTRY ABB=ON  "L-CITRULLINE HYDROCHLORIDE"/CN
L6             2 SEA FILE=REGISTRY ABB=ON  (L3 OR L4 OR L5)
L41          181 SEA FILE=USPATFULL ABB=ON  L6
L112           1 SEA FILE=REGISTRY ABB=ON  NITROGLYCERIN/CN
L116         808 SEA FILE=USPATFULL ABB=ON  L112
L117           2 SEA FILE=USPATFULL ABB=ON  L41 AND L116


=> s l117 not l58

L131           0 L117 NOT L58

=> fil medl; d que l120; d que l123

FILE 'MEDLINE' ENTERED AT 13:24:05 ON 23 SEP 2004

 FILE LAST UPDATED: 22 SEP 2004 (20040922/UP).  FILE COVERS 1951 TO DATE.

 On February 29, 2004, the 2004 MeSH terms were loaded.  See HELP RLOAD
 for details. OLDMEDLINE now back to 1951.

 MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the
 MeSH 2004 vocabulary.  See http://www.nlm.nih.gov/mesh/ and
 http://www.nlm.nih.gov/pubs/techbull/nd03/nd03_mesh.html for a
 description of changes.

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.


L59         2100 SEA FILE=MEDLINE ABB=ON  CITRULLINE/CT
L65          274 SEA FILE=MEDLINE ABB=ON  L59(L)(AD OR PD OR PK OR TU)/CT
L118        9524 SEA FILE=MEDLINE ABB=ON  NITROGLYCERIN/CT
L120           0 SEA FILE=MEDLINE ABB=ON  L65 AND L118



L59         2100 SEA FILE=MEDLINE ABB=ON  CITRULLINE/CT
L64        23202 SEA FILE=MEDLINE ABB=ON  NITRIC-OXIDE SYNTHASE/CT
L65          274 SEA FILE=MEDLINE ABB=ON  L59(L)(AD OR PD OR PK OR TU)/CT
L121       64864 SEA FILE=MEDLINE ABB=ON  NITRO COMPOUNDS+NT/CT
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L123          1 SEA FILE=MEDLINE ABB=ON  L65 AND L121 AND L64


=> s l123 not l74

L132          1 L123 NOT L74

=> fil embase; d que l125

FILE 'EMBASE' ENTERED AT 13:24:06 ON 23 SEP 2004
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 FILE COVERS 1974 TO 16 Sep 2004 (20040916/ED)

 EMBASE has been reloaded. Enter HELP RLOAD for details.

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.


L75         2121 SEA FILE=EMBASE ABB=ON  CITRULLINE/CT OR CITRULLINE DERIVATIVE/
                 CT
L93          103 SEA FILE=EMBASE ABB=ON  L75(L)(DT OR PD OR AD OR DO)/CT
L124       20944 SEA FILE=EMBASE ABB=ON  GLYCERYL TRINITRATE/CT
L125           1 SEA FILE=EMBASE ABB=ON  L93 AND L124


=> s l125 not l94

L133          1 L125 NOT L94

=> fil DRUGU, PASCAL, BIOSIS, WPIDS; d que l128

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L95         6253 SEA CITRULLINE OR NSC27425 OR NSC 27425
L102          53 SEA L95(5A)(FED OR FEED? OR ADMIN?)
L126       25343 SEA NITROGLYCERIN# OR GLYCERYL(W)(TRI NITRATE OR TRINITRATE)
L128           1 SEA L102 AND L126


=> s l128 not l108

L134          0 L128 NOT L108

=> dup rem l132,l130,l133
FILE 'MEDLINE' ENTERED AT 13:24:50 ON 23 SEP 2004
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FILE 'CAPLUS' ENTERED AT 13:24:50 ON 23 SEP 2004
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PROCESSING COMPLETED FOR L132
PROCESSING COMPLETED FOR L130
PROCESSING COMPLETED FOR L133
L135 4 DUP REM L132 L130 L133 (0 DUPLICATES REMOVED)
ANSWER '1' FROM FILE MEDLINE
ANSWERS '2-3' FROM FILE CAPLUS
ANSWER '4' FROM FILE EMBASE

=> d iall 1; d ibib ed ab hitrn 2-3; d iall 4; fil hom

L135 ANSWER 1 OF 4 MEDLINE on STN
ACCESSION NUMBER: 1998431938 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9755132
TITLE: Cyclooxygenase-2 participates in tubular flow-dependent afferent arteriolar tone: interaction with neuronal NOS.
AUTHOR: Ichihara A; Imig J D; Inscho E W; Navar L G
CORPORATE SOURCE: Department of Physiology, Tulane University School of Medicine, New Orleans, Louisiana 70112-2699, USA.
CONTRACT NUMBER: HL-18426 (NHLBI)
SOURCE: American journal of physiology, (1998 Oct) 275 (4 Pt 2) F605-12.
Journal code: 0370511. ISSN: 0002-9513.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199811
ENTRY DATE: Entered STN: 19990106
Last Updated on STN: 20021219
Entered Medline: 19981119

ABSTRACT:
To delineate the microvascular role of cyclooxygenase-2 (Cox-2) in modulating tubuloglomerular feedback (TGF) signals and to determine its relationship to neuronal nitric oxide synthase (nNOS), afferent (AA) and efferent (EA) arteriolar diameters of rat kidneys were assessed using the blood-perfused juxtamedullary nephron technique. The Cox-2 inhibitor NS-398 (10 microM) did not alter AA diameters in untreated kidneys but significantly constricted AAs by 17.0 +/- 2.2% in kidneys treated with 10 mM acetazolamide, which enhances TGF-mediated AA constriction by increasing distal volume delivery. The NS-398-induced AA constriction was prevented after interruption of distal delivery by transection of the loops of Henle. The effect was selective for AAs since NS-398 did not influence EAs of untreated or acetazolamide-treated kidneys. Pretreatment with the nNOS inhibitor S-methyl-L-thiocitrulline (10 microM) prevented the NS-398-induced AA constriction observed during acetazolamide treatment. Although we previously demonstrated that acetazolamide treatment enhanced AA constrictor response to S-methyl-L-thiocitrulline, the enhancement by acetazolamide was inhibited by pretreatment with 10 microM NS-398 (16.4 +/- 1.9 and 15. 0 +/- 0.5% with and without acetazolamide, respectively, P > 0.05). These results indicate that, during increased activation of TGF-dependent vasoconstrictor signals, Cox-2 generates vasodilatory metabolites in response to increased nNOS activity and thus participates in the counteracting modulation of TGF-mediated AA constriction.

CONTROLLED TERM: Check Tags: Male; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
Acetazolamide: PD, pharmacology
Animals
Arterioles: DE, drug effects
*Arterioles: PH, physiology
Citrulline: AA, analogs & derivatives
Citrulline: PD, pharmacology
*Cyclooxygenase Inhibitors: PD, pharmacology
Enzyme Inhibitors: PD, pharmacology
Feedback
*Isoenzymes: ME, metabolism
Juxtaglomerular Apparatus: BS, blood supply
Juxtaglomerular Apparatus: PH, physiology
Kidney Tubules: BS, blood supply
*Kidney Tubules: PH, physiology
Kinetics
Loop of Henle: PH, physiology
*Muscle Tonus
Muscle, Smooth, Vascular: DE, drug effects
*Muscle, Smooth, Vascular: PH, physiology
Nephrons: BS, blood supply
Nephrons: PH, physiology
***Nitric-Oxide Synthase: ME, metabolism**
***Nitrobenzenes: PD, pharmacology**
*Prostaglandin-Endoperoxide Synthase: ME, metabolism
Rats
Rats, Sprague-Dawley
*Sulfonamides: PD, pharmacology
Thiourea: AA, analogs & derivatives
Thiourea: PD, pharmacology
Vasoconstriction: DE, drug effects

CAS REGISTRY NO.: 123653-11-2 (N-(2-cyclohexyloxy-4-nitrophenyl)methanesulfonamide); 156719-41-4 (S-methylthiocitrulline); 372-75-8 (Citrulline); 59-66-5 (Acetazolamide); 62-56-6 (Thiourea)

CHEMICAL NAME: 0 (Cyclooxygenase Inhibitors); 0 (Enzyme Inhibitors); 0 (Isoenzymes); 0 (Nitrobenzenes); 0 (Sulfonamides); EC 1.14.13.- (neural constitutive nitric oxide synthase); EC 1.14.13.39 (Nitric-Oxide Synthase); EC 1.14.99.- (cyclooxygenase 2); EC 1.14.99.1 (Prostaglandin-Endoperoxide Synthase)

L135 ANSWER 2 OF 4 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:936088 CAPLUS
DOCUMENT NUMBER: 136:31733
TITLE: Method of treatment and prevention of nitric oxide deficiency-related disorders with citrulline and citrulline derivatives
INVENTOR(S): Chwalisz, Kristof; Garfield, Robert E.; Shi, Shao-Quing
PATENT ASSIGNEE(S): Germany
SOURCE: U.S. Pat. Appl. Publ., 17 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2001056068	A1	20011227	US 1998-34351	19980304

PRIORITY APPLN. INFO.: US 1998-34351 19980304

ED Entered STN: 28 Dec 2001

AB The invention provides methods for control, management, treatment and prevention of conditions related to nitric oxide deficiency such as hypertension, cardiovascular disease, osteoporosis, diabetes mellitus, preeclampsia HELLP, syndrome and fetal growth retardation; uterine contractility disorders such as preterm labor and dysmenorrhea, cervical dystocia, infertility and early pregnancy loss; male impotence; urinary incontinence; intestinal tract disorders (e.g. altered motility and pyloric stenosis), respiratory system diseases (e.g. asthma, neonatal respiratory distress syndrome, pulmonary hypertension, and adult respiratory distress syndrome); inflammatory diseases (e.g. acute inflammation, resistance to infection, SLE-lupus, anaphylactic reaction, allograft rejection); Alzheimer's disease, stroke, growth hormone disorders, and behavior changes; dermatol. conditions such as atopic eczema, topical hair loss, and burn injury; by administering citrulline or a citrulline analog, optionally in combination with other enhancing or modulating agents, e.g., an estrogenic, partial estrogenic, progestagenic, or androgenic agent, and pharmaceutical prepns. for such uses.

IT **55-63-0**, Nitroglycerin **372-75-8**, L-Citrulline
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(method of treatment and prevention of nitric oxide deficiency-related disorders with citrulline and citrulline derivs.)

L135 ANSWER 3 OF 4 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1994:570568 CAPLUS
DOCUMENT NUMBER: 121:170568
TITLE: The use of nitric oxide-delivering compounds for the treatment or prevention of alcoholic liver injury
INVENTOR(S): Nanji, Amin; Stamler, Jonathan; Loscalzo, Joseph
PATENT ASSIGNEE(S): Brigham and Women's Hospital, USA; New England Deaconess Hospital
SOURCE: PCT Int. Appl., 24 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9416740	A1	19940804	WO 1994-US970	19940127
W: AU, CA, JP				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
AU 9462327	A1	19940815	AU 1994-62327	19940127

PRIORITY APPLN. INFO.: US 1993-12135 19930129
WO 1994-US970 19940127

ED Entered STN: 15 Oct 1994

AB Nitric oxide-delivering compds., e.g. S-nitrosothiols, are administered to an individual for the treatment or prevention of liver disease induced by ingestion of alc., or exposure to pharmacol. agents or industrial toxins. In addn. alc.-induced liver disease may also be prevented by administering a therapeutically effective amt. of either arginine, an arginine analog, or a nitric oxide-delivering compd., in combination with an alc. beverage which is to be consumed by an individual. Rats were fed either corn oil or satd. fats with EtOH for 4 wk then sacrificed. The decrease in nitric oxide was directly proportional to the increase in liver pathol., e.g. the

amt. of nitrite concn. in rats fed with satd. fats and EtOH was 17.0 as compared with 2.8 mM for those who were fed with corn oil and EtOH.

IT **55-63-0**, Nitroglycerin **372-75-8**, Citrulline
RL: BIOL (Biological study)
(prevention and treatment of liver injury with)

L135 ANSWER 4 OF 4 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 2003378841 EMBASE
TITLE: Brain nitric oxide and its dual role in neurodegeneration/neuroprotection: Understanding molecular mechanisms to devise drug approaches.
AUTHOR: Contestabile A.; Monti B.; Contestabile A.; Ciani E.
CORPORATE SOURCE: A. Contestabile, Department of Biology, University of Bologna, Via Selmi 3, 40126 Bologna, Italy. acontest@alma.unibo.it
SOURCE: Current Medicinal Chemistry, (2003) 10/20 (2147-2174). Refs: 256
ISSN: 0929-8673 CODEN: CMCHE7
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 008 Neurology and Neurosurgery
029 Clinical Biochemistry
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
ABSTRACT:

Nitric oxide (NO) has been established as an important messenger molecule in various steps of brain physiology, from development to synaptic plasticity, learning and memory. However, NO has also been viewed as a major agent of neuropathology when, escaping controlled production it may directly or indirectly promote oxidative and nitrosative stress. The exact borderline between physiological, and therefore neuroprotective, and pathological, and therefore neurodegenerative, actions of NO is a matter of controversy among researchers in the field. This is reflected in the present status of drug research, that is focused on finding ways to block NO production, and therefore limit neuropathology, as well as on finding ways to increase NO availability and therefore elicit neuroprotection. As an unavoidable consequence, both classes of drugs are reported to have neurodegenerative or neuroprotective effects, depending on the models in which they are tested. Aim of the present paper is to provide the reader with a survey, as much complete as possible, on the main aspects of NO biology, from biochemistry and chemical reactivity to the molecular signals elicited in neural cells target of its neurodegenerative or neuroprotective action. In doing that, many controversial aspects related to basic biology and to neuropathology of NO are taken into account. In the final sections, main classes of drugs able to interfere with NO physiopathology are examined, in order to try to devise possible directions for future NO-based therapeutical strategies.

CONTROLLED TERM: Medical Descriptors:
*nerve degeneration: ET, etiology
*neuroprotection
*drug design
signal transduction
brain function
nerve cell plasticity

learning
memory
oxidative stress
biochemistry
nerve cell
neuropathology
pathophysiology
drug release
drug selectivity
hypotension: SI, side effect
enzyme structure
enzyme regulation
protein protein interaction
neurotransmission
nitration
lipid peroxidation
DNA damage
nerve cell necrosis
inflammation: ET, etiology
oxidation reduction state
neurotoxicity
human
nonhuman
review
Drug Descriptors:
*nitric oxide: EC, endogenous compound
*nitric oxide donor: AE, adverse drug reaction
*nitric oxide donor: DV, drug development
*nitric oxide donor: PD, pharmacology
*nitric oxide synthase inhibitor: DV, drug development
*nitric oxide synthase inhibitor: PD, pharmacology
*nitric oxide synthase inhibitor: IP, intraperitoneal drug administration
arginine derivative: DV, drug development
arginine derivative: PD, pharmacology
n(g) methylarginine: DV, drug development
n(g) methylarginine: PD, pharmacology
n(g) nitroarginine: DV, drug development
n(g) nitroarginine: PD, pharmacology
n(g) nitroarginine methyl ester: DV, drug development
n(g) nitroarginine methyl ester: PD, pharmacology
citrulline: DV, drug development
citrulline: PD, pharmacology
n5 (1 iminoethyl)ornithine: DV, drug development
n5 (1 iminoethyl)ornithine: PD, pharmacology
n6 (1 iminoethyl)lysine: DV, drug development
n6 (1 iminoethyl)lysine: PD, pharmacology
aminoguanidine: DV, drug development
aminoguanidine: PD, pharmacology
thiourea derivative: DV, drug development
thiourea derivative: PD, pharmacology
3 bromo 7 nitroindazole: DV, drug development
3 bromo 7 nitroindazole: PD, pharmacology
7 nitroindazole: DV, drug development
7 nitroindazole: PD, pharmacology
7 nitroindazole: IP, intraperitoneal drug administration
imidazole derivative: DV, drug development
imidazole derivative: PD, pharmacology
fullerene derivative: CB, drug combination
fullerene derivative: DV, drug development
fullerene derivative: PD, pharmacology

alpha tocopherol derivative: CB, drug combination
alpha tocopherol derivative: DV, drug development
alpha tocopherol derivative: PD, pharmacology
tamoxifen: PD, pharmacology
1,2,3,6 tetrahydro 1 methyl 4 phenylpyridine
glutamic acid
glyceryl trinitrate: AE, adverse drug reaction
glyceryl trinitrate: PK, pharmacokinetics
glyceryl trinitrate: PD, pharmacology
nitroprusside sodium: PK, pharmacokinetics
nitroprusside sodium: PD, pharmacology
isosorbide dinitrate: PK, pharmacokinetics
isosorbide dinitrate: PD, pharmacology
s nitrosothiol: PK, pharmacokinetics
s nitrosothiol: PD, pharmacology
n acetyl s nitrosopenicillamine: PK, pharmacokinetics
n acetyl s nitrosopenicillamine: PD, pharmacology
s nitrosoglutathione: PK, pharmacokinetics
s nitrosoglutathione: PD, pharmacology
membrane lipid: PD, pharmacology
nonsteroid antiinflammatory agent: AE, adverse drug reaction
nonsteroid antiinflammatory agent: PD, pharmacology
acetylsalicylic acid: AE, adverse drug reaction
acetylsalicylic acid: PD, pharmacology
unindexed drug

CAS REGISTRY NO.: (nitric oxide) 10102-43-9; (n(g) methylarginine) 156706-47-7, 17035-90-4; (n(g) nitroarginine) 2149-70-4; (n(g) nitroarginine methyl ester) 50903-99-6; (citrulline) 372-75-8; (n5 (1 iminoethyl)ornithine) 36889-13-1; (n6 (1 iminoethyl)lysine) 53774-63-3; (aminoguanidine) 1068-42-4, 2582-30-1, 79-17-4; (7 nitroindazole) 2942-42-9; (tamoxifen) 10540-29-1; (1,2,3,6 tetrahydro 1 methyl 4 phenylpyridine) 28289-54-5; (glutamic acid) 11070-68-1, 138-15-8, 56-86-0, 6899-05-4; (glyceryl trinitrate) 55-63-0; (nitroprusside sodium) 14402-89-2, 15078-28-1; (isosorbide dinitrate) 87-33-2; (n acetyl s nitrosopenicillamine) 79032-48-7; (s nitrosoglutathione) 57564-91-7; (acetylsalicylic acid) 493-53-8, 50-78-2, 53663-74-4, 53664-49-6, 63781-77-1

CHEMICAL NAME: Aspirin

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